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THE ADRENAL PROBLEM*

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We meet for the exchange of ideas in one of the most fascinating fields of biology, one which taxes the ingenuity of biologists, chemists and clinicians to the utmost. We seek facts that we may approach a little nearer the truth concerning humoral integration. Like explorers in a new country, we are finding the paths so numerous and devious that no individual can follow the course of all. Let us tramp some of the trails which have been blazed toward an understanding of two glands upon which we depend for our very existence.

For the past eighty years there has been a growing conviction that the adrenal locked up one of the major biological secrets of the higher animals. The work that has been done since the discovery of epinephrin has made a beaten path of the medulla. Although the adrenal cortex and medulla are so intimately associated, they are distinct in origin and continue to act separately in many ways throughout life. The short-lived cells of the cortex originating in the outer levels, finish their existence in the reticular zone (1). Played upon by various stresses these cells are continually being renewed without parallel changes in the medulla. Control of the two tissues likewise is apparently independent, the former humoral, the latter nervous. We are not prepared to investigate the possibility of cortical-medullary interrelationship further until more is known about the cortex.

Workers wandering away from the medullary highway discovered that the cortex was the vital part of the gland. Eleven years later in October, 1927, two groups (2) first published evidence for the existence of a vital hormone. Figure 1 compares that evidence. After a period of more than two years, improvements in the preparation of cortical extract first by Swingle and Pfiffner (3) and then by Hartman and Brownell (4) made it possible to maintain the life of adrenalectomized animals indefinitely. Many investigators have since entered the cortical field.

Progress in the isolation of the vital hormone depends upon the test employed to show its presence. No substitute has been found for com-

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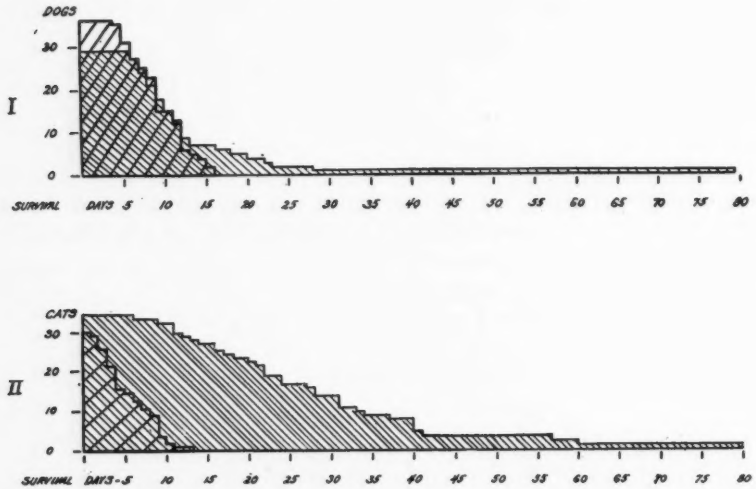
pletely adrenalectomized animals. The cat or dog test is more crucial than the rat test, although the latter can be used if need for the hormone is demonstrated in each individual instance. It is not necessary to prove long survival of the cat or dog under each dosage but the response of each individual to inadequate cortin must be known. Sensitive animals will respond within a week. However, repeated fractionation of the dosage to determine the minimum makes the test laborious. Failure to observe these precautions in testing has led to erroneous conclusions in chemical studies on cortin.



Potency of early extracts of the adrenal cortex tested on adrenalectomized animals

I Compiled from data by Rogoff and Stewart Am. Jour. Physiol., 1928, vol. 84, 663-664

II Compiled from experiments by Hartman and Brownell

Control *Extract Injected*

Although there may be a number of hormones in the cortex there is possibly only one vital hormone. Let us examine some of its properties. Cortin plays an important rôle in the maintenance of plasma volume. The volume reduction in the absence of the hormone is explained neither by loss of fluid through the kidneys nor by decreased intake, because the same results in water balance can be obtained by gradually reducing the food intake in normal animals (cats) without producing symptoms (5). There must be a redistribution of water in the body of cortin insufficient animals. How this is produced is unanswered, but we know that sodium

and chloride escape in abnormal amounts through the kidneys. This leads to a shift of electrolytes in the body. Although these losses may be significant there are other changes more fundamental for it is sometimes possible to bring about recovery from collapse by the injection of cortin without the additional administration of water and electrolytes. Although an increased intake of sodium chloride ameliorates the symptoms of early adrenal insufficiency it is unavailing in the late stage.

Cortin is necessary not only for the proper function of the digestive system but it may bear some relation to nutrition. Extracts containing this hormone but practically free (less than one-tenth of the protective dose) from vitamin C delay the onset of scurvy if one administers the extract at the beginning of vitamin C deprivation. Cortin-containing extracts afford similar protection in vitamin B_1 deficiency. On the other hand, a well-balanced diet enables rats to withstand better the removal of the adrenals without the development of symptoms (6). Likewise the diffusion properties of muscles from adrenalectomized rats so fed approach more nearly the normal than do those from adrenalectomized rats fed a less well-balanced diet (7).

The relation of the adrenals to metabolism is only vaguely understood. Their removal in most animals results in a fall in metabolism. However, in the rabbit and mouse (8) the reverse may be true as long as the thyroids are intact. This might be due to presence of accessory tissue as injury to the adrenals has been found to produce a similar effect (Marine and Baumann). The adrenal bears some relation to carbohydrate metabolism. Increased insulin in the blood seems to release more epinephrin (9). On the other hand, animals without their adrenals are much more sensitive to insulin. Experimental diabetes is much less marked in adrenal insufficiency than in normal animals. This is due at least in part to the absence of cortin (10). In adrenal insufficiency glycogen is very slowly regenerated after severe fatigue (11). In late stages of insufficiency the liver and muscle glycogen are much depleted and blood sugar usually falls.

The vital hormone affects the nervous system. Among the earliest symptoms to appear in Addison's disease are the lowered resistance to mental fatigue and increased irritability. Cortin abolishes these symptoms. It has been noted that patients with no obvious adrenal disease may show greater resistance to fatigue, both mental and physical and become more hopeful in their outlook on life after treatment with cortin. Indeed in some individuals nervous fatigue is transformed into a sense of well-being even to the point of euphoria, after cortin administration. These effects are most apparent during recuperation from certain exhausting infections.

Cortin seems to act in a contrary fashion to epinephrin. While it is "soothing and restful" the latter is "disturbing and stimulating." This has been shown by experiments on "neurotic" sheep (12). The neurosis was established by attempting too fine a discrimination in the development of a conditioned reflex. The sheep became agitated and nervous, changing from a docile to a very refractory animal. Between tests the animal, for-

merly quiet, exhibited spontaneous movements, while at the test the response to the conditioned stimulus was very weak. This "neurosis" lasts for years in sheep, once it is established. It is similar to a condition which may develop in the human being, from too much stimulation.

Repeated injections of epinephrin into "neurotic" sheep made them worse, while injections of cortin made them behave more like normal individuals. They became more docile. Nervous leg movements between tests were nearly abolished and the response to the metronome was increased. The beneficial effects of cortin were cumulative and persisted for three weeks or longer.

Abolition of fatigue, the outstanding symptom of Addison's disease, by cortin, is significant. This does not seem to be due entirely to effects on circulation, general nutrition and the nervous system; local changes in the muscles are involved.

The resistance of intact muscles to fatigue after cortin injections has been studied in the human being by means of an ergometer (13). Positive effects were obtained in widely varying clinical cases, as well as in some normal individuals. In the normal dog it has also been demonstrated that cortin therapy will increase resistance to fatigue (14). These effects may outlast the injections by several days so that some very fundamental changes in the organism must be produced.

Students of adrenal physiology have sought for years to produce chronic insufficiency experimentally. This can best be done by the administration of inadequate doses of cortin in adrenalectomized animals. After observing many animals with chronic insufficiency so produced, we conclude that failure of appetite and increased fatigability are the earliest symptoms to develop. Pigmentation has never been observed except in the monkey (15).

We have kept cats for approximately two years, without their adrenals, one a few days less, another a little longer, by cortin injections. They finally died of infections. The picture presented in chronic adrenal insufficiency is not greatly different from that observed in adrenalectomized animals during their normal survival period without cortin.

It is going to be exceedingly difficult to prove that merely one underlying change of function is responsible for the developments which occur in cortin insufficiency. The observations available indicate the involvement of many tissues of the organism, therefore the theory that cortin is a general tissue hormone seems to be more tenable.

Increased activity influences the cortex of the adrenal. Exercise, caloric demands of cold, defense against toxins or infections, excessive output of insulin, increase of thyroxin, growth processes, all induce enlargement of this tissue. The knowledge that all of these conditions likewise increase the demand for cortin in adrenalectomized animals would lead us to believe that the cortex reacts in this way to produce more cortin.

There are evidences for the production of other hormones by the adrenal cortex. The precocious sexual development which accompanies cer-

tain cortical tumors cannot be explained at the present time by an increase in the output of cortin. The need of lactating female rats for a second factor to maintain a milk supply indicates another hormone. The extension of our knowledge concerning additional hormones of the adrenal cortex awaits the discovery of better physiological tests.

Because of the vital nature of the cortex, its destruction and hypertrophy as a result of disease or stress, are important questions in medicine. In autopsies on cases of Addison's disease, cortical tissue that has escaped destruction shows little or no signs of compensatory enlargement. In young, healthy animals removal of part of the adrenal tissue leads to hypertrophy of the remainder but never sufficiently to compensate for the loss, even in the rat, in which the increase is greatest. We have found that excision of part of one adrenal and then, several months later, removal of the second adrenal in the cat, leads to little or insignificant hypertrophy. This is true even if six months is allowed to elapse after removal of the second adrenal. Animals, in which accessory adrenal bodies are the sole tissue present for several months, never show adequate hypertrophy. Such animals often die suddenly, many months after double adrenalectomy.

Is the whole of the cortical tissue needed? Perhaps not during quiet life, but under great stress, not only the normal amount of tissue is needed, but more could be used to advantage. If animals are placed under stress one whole adrenal may not be sufficient. We have found that rats from which one adrenal has been removed die within a few weeks when kept continuously at a temperature of 4° C. The remaining adrenal increased in size 50 to 150 per cent. Rats of similar age with intact adrenals survive indefinitely under the same conditions.

The question of interrelationship is very intriguing. If the anterior hypophysis controls the cortex, why does compensatory growth of the latter fail to be adequate following its partial destruction? Assumption that the potency of the hypophysis is undiminished would seem justified. Apparently we do not know the whole story. Relations of the adrenal with other endocrine organs are just as imperfectly understood.

Solution of the adrenal problem is bound inseparably to the unraveling of many normal physiological phenomena. For example, we cannot understand why electrolyte balance is upset in adrenal insufficiency until we know more about diffusion in the normal living organism.

The adrenal challenges investigators as few other organs have done. It promises revelations to those who persevere. Indeed it locks within its walls one of the major biological secrets of the higher animals.

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AN ATYPICAL FAMILIAL ENDOCRINOPATHY IN MALES WITH A SYNDROME OF OTHER DEFECTS*

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Two cases of an atypical familial endocrinopathy are presented, which were observed over a period of four years and when first seen were thought to be instances of hypothyroidism. Further observation revealed optic neuritis, limited joint extension, skeletal defects and normal mentality, which were not consistent with hypothyroidism. The autopsy on the older brother (W. W.) did show evidence of hypothyroidism and hypopituitarism.

Very few cases resembling those being reported have been found in a search of the literature. Charles Hunter (1) of England in 1917, in an article entitled "A Rare Disease in Two Brothers," described two cases almost identical with those of the author. In 1934, David and Currier (2) in this country, and Ellis (3) in England, reported cases in brothers which very closely resembled Hunter's and the author's case. David and Currier diagnosed their cases as "Morquio's Disease" and Ellis thought his cases represented the Helmholz-Harrington syndrome. An autopsy of one of Ellis' cases revealed hydrocephalus, cerebral hemorrhage, hepatosplenomegaly and fatty degeneration of the liver.

Marriott (4), who saw W. W. and R. W. in 1932, had seen two similar unrelated boys, one of whom he had been following many years, and who finally developed a much enlarged sella turcica.

The only other cases which resemble the author's are those reported by Leri (5) in 1921, and that presenting the Helmholz-Harrington syndrome, reported in 1931 (6). Leri diagnosed his cases as pleonosteosis, essentially a disease of the skeletal system characterized by great width of the cortical bone, but an otherwise normal skeleton. It is familial and although devoid of other bodily defects, the disease resembles the one about to be described. The case with the Helmholz-Harrington syndrome may possibly be a subtype of the pleonosteosis or of the disease condition presented by the brother (R. W.).

REPORT OF CASES

Case I. W. W., a white male, aged 6½ years, was first seen in August, 1930, because of defective hearing and speech. Essential points in the family history were hyperthyroidism in the mother during the patient's first year, a similarity of the child's and father's hands and an apparent auditory defect in both siblings. There was no other history of endocrinopathy or of congenital defects.

*Autopsy report by Charles T. Rosson, M.D.

The pregnancy and birth were normal but the patient did not regain his birth weight until the age of four months because of an intermittent diarrhea. He was nursed for four months and received no extra vitamins during his first year. Disturbances characterized by fever, vomiting and large, light colored or bloody stools, continued throughout his life though they were less frequent and protracted in his later years. During attacks he would lose weight though his abdomen was protuberant and he appeared to be overweight. Tests for causes of these disturbances were not informative. At two years of age he began to walk but had not talked. His frenulum was clipped at the age of four months and again at two years to encourage talking. In spite of his physical disabilities he had a normal mentality, learned to read lips without instruction, and to convey his thoughts by action and by very limited speech with a husky unresonant voice. There was no history of convulsions. He had no abnormal habits except enuresis and inactivity. He was circumcized at the age of four years. His tonsils and adenoids were removed in his second and fourth years because of frequent respiratory infections, which were accompanied by tender, auricular swellings, causing pain on eating as in Mikulicz's syndrome but there was no otalgia or otorrhea. He had bronchitis occasionally and dyspnea rarely, but there was no history of rheumatism or chorea. From the age of three to four and one-half years he was given thyroid extract. It was discontinued because of nervousness. His mother noted slight benefit to skin, hair and general activity.

Physical Examination. His general appearance was that of a boy of retarded physical development with a serious expression, a full and puffy facies and skin which was thick, coarse and freckled. The following were his measurements at the age of 6½ years: weight, 46 lbs. (49 lbs. ideal weight); height, 43½ inches (low normal); span 41 inches (short); lower, 20¾ inches and upper, 22¾ inches; chest, 24 inches. (See Figure 1 for general appearance.) He had a dolichocephalic skull with a circumference of 21½ inches (ideal 20½ inches). In the axillae and on the extensor surfaces of the arms there were numerous nodules which were raised, round, white, firm, non-tender, circumscribed and discrete. There were a few small, hard cervical nodes. The mucosae were normal. His eyes and nose were normal. The ear drums were gray and retracted, but there was a slight amount of bone conduction, with a middle C note. The otologists could not determine whether the deafness was congenital or acquired. There were several carious teeth and spots deficient in enamel but his tooth age was normal. His tonsil tags were growing. A large, thick, rough and red tongue obstructed the pharyngeal view. Thyroid tissue could not be felt in the neck. There were no signs of rickets. His lungs, heart and blood vessels were entirely normal; the pulse rate was 80 and blood pressure 110/70. The abdomen was enlarged. The liver was four and the spleen eight finger breadths enlarged, and both viscera were enlarged, smooth, firm and non-tender. His genitalia were normal. Neurological findings were normal. His hands and feet were small and his fingers as in the trident hand were short, thick, square at the ends and partially flexed.

Laboratory Data. The first blood examination showed 4,440,000 red cells; 95 per cent hemoglobin; 5,300 white cells; 43 per cent polymorphonuclear cells; 16 per cent large lymphocytes; 31 per cent small lymphocytes and 9 per cent mononuclear cells. The platelets and cells were normal in appearance. The serum calcium was 10.5 mg. per hundred cubic centimeters. The glucose tolerance test showed the following blood sugar values per hundred cubic centimeters of blood; fasting 88 mg., one-half

hour, 120 mg.; one hour, 132 mg.; two hours, 98 mg.; three hours, 85 mg. The blood and spinal fluid Wassermann reactions were negative. The urine, stool, and spinal fluid analyses were normal and the tuberculin reaction was negative. The basal metabolic rate was 12.6 per cent plus by the Benedict-Talbot standard. A biopsy of the skin showed subcutaneous fibrosis without scleroderma or myxoedema.

Roentgenogram Examination. The bone age was four years at the highest, an osseous retardation of over two years. The sella turcica was slightly smaller and more shallow than normal. There were no other abnormalities. A slightly enlarged shadow in the upper mediastinum did not justify the diagnosis of enlarged thymus. The heart and lungs appeared to be normal.

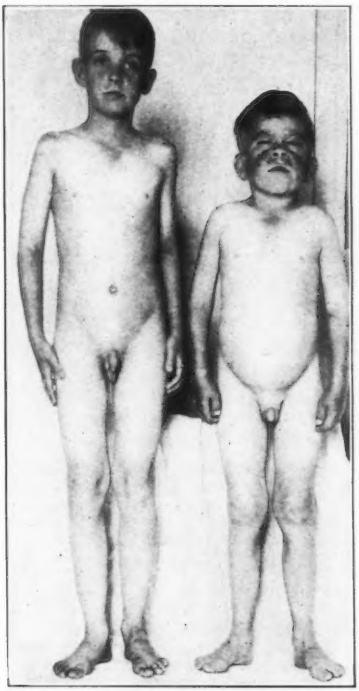

Figure 1. Patient W. W., on the right aet. 8 years, with normal control.

Mental Examination. The intelligence quotient was over 100 per cent.

Course and Treatment. The patient had frequent subnormal temperatures, as low as 35.6° C.; his pulse ranged between 70 and 80 and he was inactive. In September, 1930, thyroid medication was instituted again. He was given one-half grain desiccated gland substance twice daily.

Progress Notes. By October, 1931, an interval of 13 months, he had grown only seven-eighths of an inch. After an attack of measles his hearing seemed to be improved temporarily, he could say a few words and his skin had fewer infiltrations. His temperature continued to be subnormal

and he wore a heavy sweater even in warm weather. His thyroid gland could not be felt and his liver and spleen were unchanged. The left optic nerve head was slightly blurred nasally. The blood cholesterol was 162 mg. per hundred cubic centimeters, he still had a moderate leukopenia (5,400) and a lymphocytosis. The thyroid dosage was increased to three grains daily. Roentgenogram examination made at the age of 8 years and three months in April, 1932, showed the absence of the scaphoid which should be present between the fifth and seventh years. The distal epiphysis of the ulna, which should have appeared at seven years, was also absent. The metacarpals, phalanges and ulna were broader than normal, a finding consistent with hypothyroidism.

On examination five months later, after having been in a state school for the deaf for a year and a half, he showed progress with words and sign language but his hearing was gone entirely. He had grown only 3 inches in 25 months of treatment. Following chickenpox he had pains in his feet and in the popliteal spaces, which interfered with his walking. Thyroxine, 0.8 mg. daily by mouth, was started. According to the ophthalmologist's examination, the right fundus showed a normal but slightly pale disc. There were small white spots near the macula with white streaks toward the disc which were considered the remains of nerve sheath covering. The disc edges of the left fundus were blurred; there was temporal pallor and papilledema of less than one diopter. Macular spotting and streaking were also present.

A gastric analysis showed 28 cc. free hydrochloric acid and a total of 53 cc. After thyroxine was omitted for a week a three-day calcium metabolism study was made but this showed no remarkable variation from the expected normal. His basal metabolic rate was 8.6 per cent. Urinalyses continued to be normal and a moderate leukopenia and lymphocytosis were still present.

In November, 1932, the impression of bilateral coxa vara was confirmed by roentgenograms. There were no other bony changes. Ten months later, at the age of 9 years and 9 months, his height was 47¾ inches and his weight 58 pounds. He had grown only 4¼ inches during three years of therapy. He had acquired some speech. Physiotherapy had relieved the pain in his heels but his skeletal deformities still caused considerable discomfort. The left optic disc was more edematous at this time. Occasionally he had a mild dyspnea but his heart was apparently normal.

On November 15, 1933, he died suddenly from pulmonary edema.

NECROPSY REPORT

The postmortem examination was performed 36 hours after death, and was made subsequent to an autopsy by the Coroner, and embalming. These facts added considerably to the difficulties of interpreting the gross and histological findings.

General examination revealed a body similar in appearance and external characteristics to that described in the clinical history.

Mediastinal and Pleural Cavities. An enlarged bilobed thymus, greyish-yellow in color and extremely soft in consistency, concealed the great vessels and the upper portion of the heart. It weighed 65 gm. and, on cut section, thick milky fluid exuded from the parenchyma.

The heart weighed 190 gm. The mitral valve was completely fused into one leaflet and there was definite mitral stenosis. The aortic valve measured 4 cm. The other valves were normal. The right chamber of the heart appeared moderately dilated.

The lungs were crepitant throughout and no areas of consolidation were found. The right lung weighed 250 gm. and the left 240 gm. A moderate amount of pulmonary edema was present.

Abdominal Cavity. There was about 250 cc. of blood-tinged fluid in the abdominal cavity. The liver extended 10 cm. below the costal margin. The spleen filled the left upper quadrant. The entire gastro-intestinal tract was normal.

The liver weighed 250 gm. after fixation. It was large, somewhat soft and pale, with a rounded border. On cut section, it showed the nutmeg appearance of passive congestion, but was softer than is usual in that condition. The gall bladder and ducts were normal.

The spleen was large and extremely soft, with a tense capsule. It weighed 590 gm. It was golden-brown in color and was much paler than a normal spleen. The pulp was soft and easily smeared. The pancreas, kidney, ureters and bladder were all normal in appearance except for post-mortem changes in the pancreas. The prostate was extremely small and infantile in appearance.

Ductless Glands. The right suprarenal gland had been partially destroyed by the previous autopsy; the left weighed 4.5 gm. and appeared to be normal. The thyroid gland weighed 5 gm.—less than half the weight of a normal gland. On cut section it showed the usual amount of colloid. No adenomata were found.

The testicles showed no unusual characteristics exeept that they were possibly smaller than usual for the patient's age.

The sella turcica appeared to be of normal size. No evidence of erosion was found. The pituitary body appeared to be normal, weighing 0.6 gm. The brain weighed 1700 gm.

MICROSCOPIC DESCRIPTION

Heart and Lungs. A few small areas of degeneration were found in the heart muscle without any surrounding reaction. No typical evidence of rheumatic myocarditis was found. The lungs showed passive congestion and moderate pulmonary edema. No evidence of pneumonia was seen.

Liver. The general architecture was intact; there was, however, a mild increase in the inter-lobular fibrous tissue. In some areas near the central veins there was rather marked passive congestion. The portal space contained an excess of lymphocytes.

Spleen. The malpighian bodies were few in number and stood out poorly. The pulp contained considerable numbers of polymorphonuclear cells and undifferentiated cells which probably were myeloblasts and myelocytes. The venous sinusoids were dilated.

The kidneys, pancreas, bladder, prostate and ureters appeared to be normal.

Testicles. Both testicles were infantile in type and uniform in appearance. Spermatocytes of the first and second order were present, but no sperm were seen. The usual number of tubules was present.

Thyroid Gland (Fig. 2). The acini varied from those of small size, containing no colloid, to those of moderate size, filled with pale-staining colloid. They were lined with flat to cuboidal and low columnar epithelium. The cell cytoplasm appeared clear and in many places had desquamated. Many of the cells appeared to be undergoing degeneration. There was no increase in the amount of lymphoid elements but there was a definite in-

crease in the interlobular connective tissue. The combined picture of a mild hyperplasia with the involutional changes suggested a gland that was attempting, unsuccessfully, to maintain adequate function.

Pituitary Body (Fig. 3). The anterior lobe showed a fairly normal relationship in regard to numbers between the chromophobe and chromophile cells. Throughout the section, however, there were areas of degeneration and necrosis which appeared to have occurred before death. The cellular degeneration appeared to be beyond that which might be expected as a postmortem change. The eosinophilic cells were best preserved. Small areas of interstitial fibrosis were encountered. An abnormal number of the acinae contained a colloid-like substance. The posterior lobe appeared normal.

Thymus. The cortex appeared well differentiated from the medulla. Hassal's corpuscles were present, but did not appear to be fused or lessened

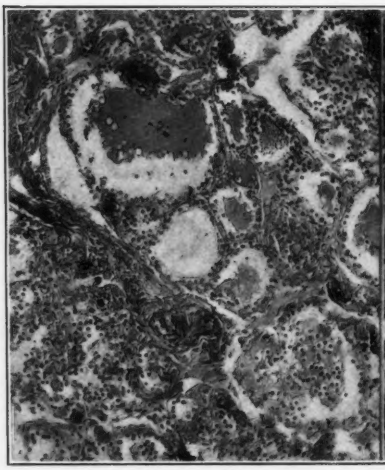

Figure 2. Thyroid gland.

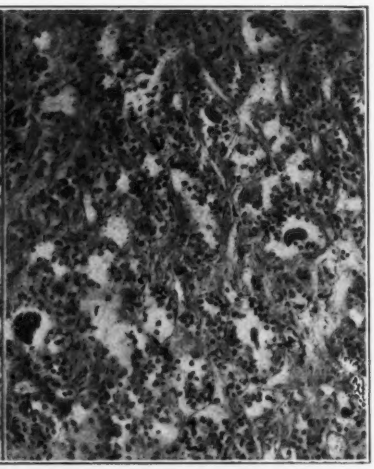

Figure 3. Pituitary gland.

in numbers. The stroma cells appeared to be lymphocytes almost exclusively. Eosinophiles were absent.

The suprarenal glands, bone marrow and central nervous system were normal except that the latter exhibited postmortem change.

Case II. R. W., brother of W. W. (Case I), was first seen at the age of 19 months (March, 1931), because of fever and cervical adenitis following measles at 17 months. Pregnancy, birth, feeding and development were normal. He had had bilateral inguinal herniae from birth. He was allergic and was subject to eczema and frequent head colds which occasionally persisted for two or three months. He had had scarlet fever at one year and chickenpox at 18 months. His hearing was decreasing and he resembled his brother closely. Otherwise, his history was not remarkable.

On entry, R. W. was 32¼ inches tall (normal), weighed 28½ pounds and had a slight general obesity. His skull, skin, hair, face, tongue, abdomen, extremities, posture and gait were like those of W. W., though less marked. (See Fig. 4.) He was suffering from a bilateral chronic purulent

otitis media and it was difficult to determine whether his defective hearing was congenital or acquired, and of nerve origin. His liver and spleen were not palpable. Laboratory examinations gave negative findings. His bone age was 1½ years.

His subsequent course was as follows: Thyroid therapy, ½ grain daily, was instituted in June, 1932, with an effect similar to that on W. W. His hearing had gradually diminished. In August his bone and chronological ages were the same. One month later, a non-tender, smooth, semi-solid spleen and liver were palpated, which were enlarged two and three finger breadths. His skin felt scleremato us. His fundi may have had an

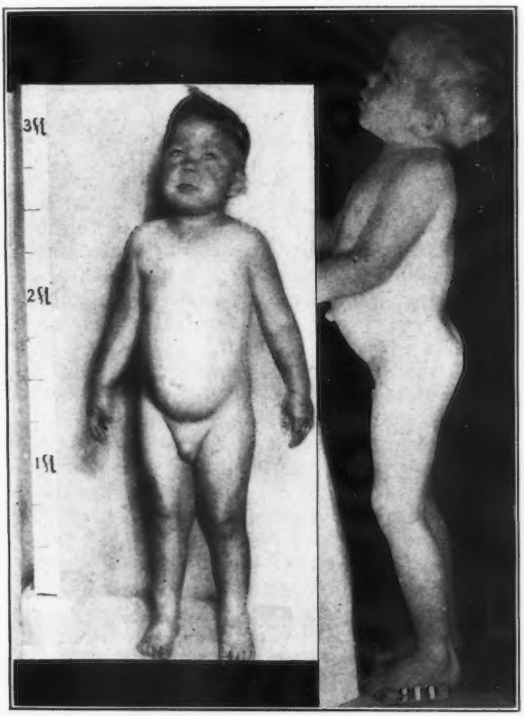

FIGURE 4
Patient R. W., aet. 2½ years.

FIGURE 5
Patient J. D.

increased number of vessels. At that time they showed slight blurring of the disc edges and pallor, and the periphery of each fundus was a bit mottled. The maculae, while somewhat cloudy, did not show definite pathology. There was a soft systolic murmur at the apex of the heart. Hematuria had occurred occasionally because of a congenital narrowing and scarring of the external urethral meatus. His tonsils and adenoids were removed in January, 1933.

Laboratory examinations gave negative findings. The blood calcium and phosphorus were within normal limits though the phosphatase was elevated. The various blood lipids were also normal. Roentgenogram ex-

amination showed some short coarse trabeculations in the metacarpal and phalangeal bones and less marked in the tarsal and metatarsal bones. The long bones appeared slightly heavy for his age. The sella turcica was within normal limits for size. His bone age was between three and four years. The intelligence quotient was 83.

In July, 1933, his height was 40 inches, age 3 years 10 months. Thyroid dosage had been increased to 1½ grains daily. His hearing and speech were becoming more deficient. The skin of his hands and face had become more markedly thickened. His liver and spleen were increasing in size and seemed more firm. The extension of his joints had diminished and he had had several attacks which resembled those recurring in Mikulicz's syndrome. During the succeeding year he grew to 42 inches and the span was 40 inches. His total growth had been four inches during two years of treatment. His chronological age was 4 years 10 months and his mental age was 3½ years. The discrepancy was attributed to the handicap of deaf-mutism. A skin biopsy showed a mild chronic non-specific dermatitis. An electrocardiogram was within normal limits. The roentgenogram examination of his chest gave normal findings.

Case III. J. D.,* aged 6 years and 3 months, first resembled the previous two cases at the age of 4 years (see Fig. 5). A physician who had seen W. W. and R. W. recognized J. D.'s similarity to these patients. His birth, feeding and development had been normal. His height was 43 inches (normal for 5 years), and he weighed 54 pounds, which was 12 pounds overweight. He had a large head, his expression was dull, though occasionally he smiled, his face was wide and his features "leonine." Most of his obesity was on the face, trunk and shoulders, and his legs were thin. His measurement from the floor to his symphysis pubis was 21.5 inches, and from vertix to symphysis 22.5 inches and his span was shortened. His neck was short and there was a mid-dorsal kyphosis. His joints were large and those of the fingers were nodular. There was limited extension of all the joints. His hands and feet were short and stubby and the backs of his hands were puffy. His skin was dry but coarse only on the trunk, arms and face. His hair was coarse and dry with an excess on the face, arms and eyebrows. The skull was dolichocephalic, 22.5 inches in diameter with large frontal bones. A low grade optic neuritis was present. He had a saddle and negroid type of nose with wide, flaring nares. The lobes of the ears were large and the canals deformed. His jaws were large and wide with large lips and tongue. He had twenty deciduous teeth, which were small and badly spaced and there was some caries. Large tonsils obstructed nasal breathing. A thyroid gland could not be felt. His lungs were normal but there was a systolic murmur over his heart. The abdomen was distended. He had a large umbilical hernia and his liver and spleen were enlarged. His intelligence quotient was 45 per cent and he was docile and quiet.

Laboratory Data. The blood study showed 5,560,000 red cells; 88 per cent hemoglobin; 7,200 white cells; 55 per cent polymorphonuclears; 33 per cent lymphocytes; and 8 per cent eosinophils. There were occasional red blood cells in the urine. Tuberculin and Wassermann reaction tests were negative. The blood calcium, phosphorus and cholesterol were within normal limits. A basal metabolic rate could not be obtained. The glucose tolerance rate was normal. The blood pressure was 103 systolic and 60 diastolic. The roentgenogram examination showed thickened dense bones in the skull and the presence of Legg's disease in both femors. Biopsy of

*Presented through the courtesy of Dr. Ethel R. Harrington of the Los Angeles Children's Hospital.

the liver showed a marked fatty infiltration but no fat in the histiocytes. Spleen puncture did not reveal splenic cells.

Treatment. Thyroid extract was instituted and the patient was sent to a school for deaf mutes.

DISCUSSION

The autopsy on W. W., while incomplete, rules out many suggested entities. The question of hypothyroidism was of the greatest interest. The deficient amount of thyroid tissue is obviously important although the microscopic picture was not entirely one of a hypofunctioning thyroid gland. The morphology of certain endocrine glands (pancreas and parathyroid especially) is, however, not a final criterion of their physiological functions. Other structures usually affected in hypothyroidism, the skin, for example, lacked typical hypothyroid findings. The colloid storage in the anterior pituitary gland is occasionally reported in hypothyroidism. Fibrous tissue growth in the gland is unusual and probably indicates hypopituitarism, which may account for some of the failure to grow. The retarded development of the epiphyses is a typical finding in hypothyroidism. On the clinical side the facies, tongue, hair, texture and appearance of the skin, and retarded growth, all suggested hypothyroidism. Against the diagnosis of hypothyroidism and hypopituitarism, and impossible to explain on that basis, were the failure of adequate therapeutic response, normal mentality, the limitation of extension, the large liver and spleen, and the thymic enlargment. An endocrinopathy does not seem to explain the following constant findings: large dolichocephalic skull, optic neuritis, deaf-mutism, the previously mentioned joint flexion, the normal mentality and the enlarged liver and spleen. These constant findings represent an independent coexistent syndrome. It was felt that rheumatic carditis had no relation to the above but was a coincident superimposed feature. However, one of Hunter's patients probably had rheumatic carditis. Marriott felt that the enlarged liver and spleen, the questionably bronzed skin, optic neuritis, tendency toward leukopenia with lymphocytosis, and a lipoid metabolic disturbance, might be suggestive of Niemann-Pick disease. Our autopsy on W. W. did not reveal any lipoid disturbance.

Ruggles (7) thought that the disturbance was an atypical or mild variety of Morquio's disease (8). However, this disease is limited to the skeleton and is a destructive type of osteochondrodystrophy. Our patients had some very suggestive findings of the radius but there were no other typical findings. Furthermore, the additional findings of facies, skin, and joint mobility changes, together with hepatosplenomegaly and leucopenia, do not occur in Morquio's disease. Leri's pleonosteosis, another purely skeletal disturbance, characterized by an overdevelopment of bone in length and thickness and premature bony development more nearly resembles the picture of the patient in question than any known entity. Leri's disease does not explain the additional findings and the retarded epiphyseal development. While the bones in the author's case were heavy and thick, they

did not fracture at any time as do those in osteosclerosis (Albers-Schönberg disease).

Weber (9) felt that these cases (W. W. and R. W.) did not appear to fit into any generally recognized group. He suggested that perhaps one might provisionally make another group headed by the type described by Helmholz and Harrington, with the author's cases as a less severe variety, and the case described by Pritchard as a minor, incomplete form. He also stated that he might be able to add some other cases, for instance, some children with enlarged livers and spleens and peculiar faces. He had in mind the cases of Hunter (1), Sheldon (11), Ellis (3), Poynton, et al. (12), to which group might be added Marriott's cases (4).

SUMMARY

Three cases are reported of a syndrome that included: familial occurrence in males of a typical physical development, having almost identical facies (resembling that in hypothyroidism); optic neuritis; normal mentality; limited extension of joints which are always partially flexed; thick, pudgy extremities; thick bones; retarded epiphyseal osteogenesis; dry, thick, coarse hair, and skin areas (on extremities particularly); abdomen enlarged because of hepatosplenomegaly; a tendency toward lymphocytic leukopenia.

In one case that came to autopsy areas of degeneration and necrosis were seen in the anterior lobe of the pituitary. The thyroid showed a picture of combined mild hyperplasia and increase of interlobular connective tissue with evidences of degeneration in many of the alveolar cells. The thymus was enlarged.

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ON THE CLINICAL USE OF EMMENIN (HUMAN PLACENTAL EXTRACT—COLLIP)*

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The correction of menstrual disorders by the use of various products of glandular origin has been tried by hundreds of workers since Knauer (1), in 1896, first demonstrated the effect of ovarian transplants on the endometrium. That the placenta might be a gland of internal secretion producing large amounts of sex hormone was first suggested by Halban (2) in 1905, but proof of this hypothesis was not forthcoming until seven years later when Iscovesco (3) demonstrated, in placental tissues, large quantities of a lipoid principle capable of producing growth and vascularity in the resting tubular tract of the rabbit. The presence of this principle, which we now know to be estrin, was soon corroborated by Aschner (4), Fellner (5), and Frank (6). Ercoli (7), in 1915, secured similar results in guinea pigs and suggested that clinical application be made of this property of placental extracts. In 1926 Zondek and Aschheim (8) succeeded in isolating a second principle from the placenta, an anterior pituitary-like gonadotropic hormone, apparently identical with that found by them in the blood and urine of pregnant women. Wiesner and Crew (9) and Collip (10) also demonstrated this substance in placenta. In 1930, however, a third and hitherto unrecognized principle was isolated by Collip and called by him, Emmenin.

"Emmenin," to quote Collip, "is an alcohol soluble, ether insoluble hydrolysable complex present in acetone extracts of human placentae, active orally and powerfully estrogenic in immature rodents with intact ovaries, though relatively inert in ovariectomized animals." It, like the first principle, estrin, is non-ovary-stimulating in its action but differs from the known forms of estrin in being (1) ether insoluble and (2) ineffective in castrates. For the latter reason, it is the opinion of Collip and his coworkers that Emmenin may be converted in the animal organism by the ovary, even the immature ovary, into some more active or potent form of estrin.

Collip and Campbell (12), after clinical trial of Emmenin in various menstrual disorders, concluded that it does not alter normal cycles; that it appears to correct certain types of amenorrhea of recent origin; that it definitely lengthens the cycles in polymenorrhea; that it relieves menopausal symptoms of recent origin but does not relieve symptoms in cas-

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†Aided by generous contributions from two anonymous friends of the Medical School.

trates; and finally that its effect in dysmenorrhea is particularly encouraging.

METHODS AND CLINICAL RESULTS

The following is a report concerning 83 patients who received Emmenin made from human placenta by the method of Collip. While these patients were treated for various menstrual disorders, particular attention was paid to dysmenorrhea, a condition in which Campbell and Collip reported 90 per cent improvement.

It must be admitted from the outset that the evaluation of the efficacy of any medication in the treatment of menstrual disturbances, and especially in the treatment of such a subjective symptom as dysmenorrhea, is beset with difficulties. One must take into consideration the spontaneous, normal variations from cycle to cycle as well as the influence of coincident and extraneous factors. In beginning this series, therefore, we used placebos for some of our patients but soon found that this procedure was unnecessary as the conditions treated were of such long duration, of such definite character, and had been treated with a sufficient variety of preparations, to rule out any mere psychic improvement. Pelvic findings, of course, were normal. In many of the cases graphic records were kept showing from month to month the interval, duration and amount of flow (estimated from the number of pads used) as well as the degree, duration and time relation of the dysmenorrhea.

The question was always asked: "Is this period any better or worse than the average period, and if better, is it better than the best period you have had without treatment?"

The use of sedatives and anodynes was not permitted except in the most extreme cases in which no relief was obtained.

The dosage was usually one teaspoonful thrice daily (given in orange juice because of the unpleasant taste and odor), increasing to six teaspoonfuls daily for one week to ten days preceding the expected period. One teaspoonful represents about 25 grams of placental tissue.

The Emmenin which we used was supplied to us from two sources: (1) through the generous cooperation of Eli Lilly & Company at the suggestion of Professor Collip, and (2) through the courtesy of Dr. Herbert M. Evans, in whose laboratory this substance was also prepared and tested for potency on rats.

The results of treatment were classified as excellent, improved, doubtful and unimproved, the criterion of improvement being invariably continued relief over a reasonable period of time and not a mere transient benefit.

Of the 83 patients treated, 17 had to be excluded from further consideration either because they did not take the preparation for a long enough period of time to justify any conclusions regarding its value, or because they failed to report again or reply to a letter of inquiry. The remaining 66 patients are grouped according to their complaints, as amen-

orrhea, polymenorrhea, hypomenorrhea or dysmenorrhea. Since some of the patients may be grouped under two different classifications simultaneously, the total number of cases may appear to be nearer 100 than 66.

Amenorrhea. There were eight patients whose principle complaint was amenorrhea. The term amenorrhea hardly needs defining but may be qualified by including only those cases not due to constitutional disease, in the ordinary sense of that term. Menstruation had not occurred for from three months to six years, the ages of the patients ranging from 17 to 40 years. Four of these patients were not improved, in one the results were doubtful, while in three cases regular menses were re-established.

The following comment may be offered regarding this group which we realize is too small to be used as a basis for forming definite conclusions. No attempt was made to classify the type of amenorrhea by hormone studies of either blood or urine since we were not equipped, at the time this work was begun, for such study. Fully cognizant of this lack and also of the probable inadequacy of the dosage for this type of case, we can still report that the failures occurred in patients whose amenorrhea had lasted from one and one-half to six years. This coincides with the experience of Collip and Campbell.

The one case, classified here as doubtful, was designated thus because, although menstrual periods occurred, they were not sufficiently regular or frequent to warrant being included under the category "excellent," a term which has been reserved for results such as these: One patient's last period occurred in June, 1930. Emmenin was started on December 20, and menstrual periods occurred in January, March, April, and May, 1931. In another case, the last period occurred in March, 1932. Emmenin was started in September, 1932, and menstruation occurred on October 25, November 18, and December 14, 1932, with normal flow.

Oligomenorrhea. The line of demarcation between oligomenorrhea (used in the sense of infrequent or delayed periods) and temporary amenorrhea, is a purely arbitrary one, depending entirely on the previous history of the patient. Of the nine patients in this category, three were completely relieved, five definitely improved and in only one was the result doubtful, this in a woman whose oligomenorrhea followed radium treatments for menorrhagia. As an instance of a patient completely relieved we cite the case of a young married woman aged 25 who had scanty, painful periods at intervals of three to four months. After six months of Emmenin therapy this patient was having regular, painless periods with better flow.

Irregular Periods. Under this classification we grouped seven patients who had absolutely irregular periods, that is to say, intervals varying from two to eight weeks in the same individual. Of these, four were improved and three became perfectly regular.

Polymenorrhea. The attempt to lengthen the interval of those whose periods occurred too frequently happened to be entirely unsuccessful in the three cases herein reported.

Hypomenorrhea. This term is used to designate scanty menses. The criterion for inclusion in this group was the use of less than three pads daily, the type of pad and personal hygiene, however, being given due consideration. There were 12 cases in this group of whom three were not improved, eight definitely improved and one completely relieved.

Menopausal Symptoms. There were eight patients, varying in age from 27 to 55, who were treated for menopausal symptoms (three of them suffering from artificial menopause). In two the results were doubtful, four patients were improved and two were completely relieved. Although this would seem quite satisfactory, we might add that many ovarian products may boast of similar success in relieving menopausal symptoms, and most of them certainly at far less expense. In view of the experimental evidence that Emmenin does not substitute for ovarian function, being relatively inert in the castrate, it is odd that one of the patients whose symptoms were definitely ameliorated was entirely minus her ovaries. Perhaps the reason for this is that the production of estrus in the test animal is not necessarily comparable to the relief of subjective symptoms in the human.

Headache. Headache of a cyclical nature was noted in seven cases. No improvement occurred in one, in two the results were doubtful, three were definitely improved and one was completely relieved.

Sterility. Sterility was a presenting complaint in four cases. Of these, two subjects became pregnant while on treatment. One of these was a woman of 34 whose sterility was of 10 years' duration.

Dysmenorrhea. There were 40 patients who complained of painful menstruation, with or without molimina. The ages ranged from 14 to 40 years, 26 of these being under 30 and 14 being 30 or over. In all of these the pain was at least moderately severe and in the great majority excruciatingly so, sufficient in most of them to require confinement in bed. Emmenin failed utterly in eight cases, was of doubtful value in seven, produced definite improvement in 12 and achieved brilliant results in 13. In other words, in 25 of 40 cases or over 60 per cent the patients were either entirely relieved or markedly improved. Seventeen or 65 per cent of those under 30 were improved as compared to eight or 57 per cent over 30.

One can hardly exaggerate the enthusiasm of those patients who experienced such remarkable relief. One patient aged 19 was in the habit of spending four or five days in bed; she was completely relieved. One patient aged 17½, whose menses had begun at 12, said: "The medicine is worth its weight in gold," and is so enthusiastic that she has been buying the Canadian commercial preparation at six dollars per four ounces (recently reduced to four dollars and twenty-five cents). She is one of the fortunate ones who can afford to pay for it. Another girl aged 14 years and 9 months could not ride in an automobile even between periods because of lower abdominal pain. Her parents could not afford to pay for the Pullman berth to bring her a great distance to San Francisco. She was mar-

velously relieved and a few months later made the long trip sitting up in a chair car. A married woman aged 34 had been sterile since her first and only pregnancy 10 years before. With each menstrual cycle she suffered intense "labor pains" associated with swelling and tenderness of the breasts and great fatigue. She was forced to remain in bed and if it was necessary for her to get up she had to crawl around on hands and knees. After a period of treatment extending over eight months she was completely relieved and subsequently became pregnant. Since delivery she has not been under treatment but her relief has been permanent.

One case of dysmenorrhea classified as a doubtful result brings up an interesting question. The patient, a single woman of 33, was relieved for a year and then, while still under treatment, had two recurrences of severe dysmenorrhea. Does this mean that the patient developed an immunity to the preparation, or perhaps an antihormone?

Miscellaneous Complaints. One patient listed does not fall into any of the above classifications. Her menses were perfectly cyclical and normal in character except that regularly on the fourth day of her period she complained of great weakness, dizziness, sinking sensations and nausea. Frequently there were noted swelling of cervical lymph nodes and on one occasion there was a transient amblyopia. These complaints would gradually subside but it would be at least a week before she felt well. This patient was greatly benefited by therapy as she was able to continue at her work during subsequent periods. Another interesting case was one of distressing vulval swelling accompanying the menstrual period. This subsided under treatment with Emmenin.

The above comments are all summarized in the following table:

MENSTRUAL DISORDERS TREATED WITH COLLIP'S EMMENIN

Complaint	Number of Cases	Results				
		Excellent	Improved	Doubtful	Unimproved	Percentage Either Partially or Completely Relieved
Amenorrhea	8	3	0	1	4	37½%
Oligomenorrhea*	9	3	5	1	0	89%
Irregular Periods	7	3	4	0	0	100%
Polymenorrhea**	3	0	0	2	1	0%
Hypomenorrhea***	12	1	8	0	3	75%
Menopause	8	2	4	2	0	75%
Headache (cyclic)	7	1	3	2	1	57%
Sterility	4	2	0	0	2	50%
Dysmenorrhea	40	13	12	7	8	62½%
Miscellaneous	2	2	0	0	0	100%

*Infrequent or delayed periods.
**Too frequent periods.
***Scanty periods.

COMMENTS

Although this relatively small group of cases forbids any sweeping conclusions, we have been impressed, from the clinical standpoint, with the excellent results and remarkable feeling of well-being experienced by many of our patients. In view of this fact and also because our findings so closely corroborate those of Campbell and Collip, it has been surprising to us to find no other reports in the literature concerning the clinical use of Emmenin besides the original communications.

We are not attempting to explain the chemico-physiological mechanism by which the results are achieved as these are not entirely clear to us. One is tempted to doubt that it can all be attributed to the administration of the hormone per se. Collip himself suggested that the favorable clinical results which he noted might be accounted for, in part, by other substances in the extract, for example, various amino acids. Apropos of this conjecture, the demonstration by Chang (14) of considerable amounts of acetyl cholin in Emmenin is most interesting since this substance is known to be a powerful stimulant of the parasympathetic nervous system.*

Attention should be called to the odd requisite of utilizing human placentae as the source of this hormone. Emmenin does not seem to be present in animal placentae, a fact which is reminiscent of the curious absence of the Aschheim-Zondek reaction in the urine of pregnant animals (except in the higher apes and during a brief period in the pregnancy cycle of the mare).

Emphasis should be placed on the fortunate circumstance that this endocrine placental extract, Emmenin, is, like thyroid, efficacious orally and so obviates the necessity of frequent hypodermic injections, an advantage which is not shared by the extracts of pancreatic islet tissue, the parathyroids, the anterior and posterior pituitary gland and the medullary and cortical portion of the adrenal glands.

Emmenin, however, is rather an expensive endocrine product for long continued use. It is manufactured commercially by a Canadian firm† and in the United States costs the patient four dollars and twenty-five cents per four ounces. This, in the dosage used by us, amounts to between fifteen and twenty dollars per month.

SUMMARY

1. Emmenin-Collip, an alcohol soluble, ether insoluble complex present in acetone extracts of human placenta has been given an adequate trial in one hundred instances of various menstrual disorders, occurring in 66 women.

2. It has proved helpful in restoring menstruation if periods have been absent less than a year. It is probably useless in amenorrhea of longer duration.

*Acetyl cholin orally is ineffective. However, some of its esters are effective when given by mouth.

†Ayerst, McKenna & Harrison, Montreal, Canada.

3. In eight of nine cases of oligomenorrhea (delayed periods) the menstrual interval was more nearly regularized. The same result was accomplished in seven patients whose menstrual interval was utterly irregular, sometimes too soon, other times too late.

4. Polymenorrhea (consistently too frequent periods) was unaffected by Emmenin (only 3 cases).

5. Hypomenorrhea (scanty flow) was definitely improved in nine of twelve cases.

6. Menopausal symptoms and cyclic menstrual headaches were relieved in a fair majority of cases.

7. In two of four cases of sterility pregnancy occurred under Emmenin therapy.

8. Over 60 per cent of 40 subjects with severe dysmenorrhea were remarkably relieved. Psychic factors were rigidly excluded. This constitutes its most significant clinical usefulness.

9. Emmenin deserves a place in the therapeutics of menstrual disorders. The chief objection, at present, to its widespread use in clinical practice, is its expense.

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THE EFFECT OF OVARIAN HORMONES AND OVARIAN GRAFTS UPON THE MAMMARY GLANDS OF MALE MICE[1]

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The function of the ovary in the stimulation of mammary gland growth was first critically demonstrated in males or ovariectomized immature females bearing ovarian grafts. The guinea pig was extensively used in these experiments as the growth of the nipples served as an easily determinable index of ovarian function. For a review of this work reference to made to Smelser (1933).

Two ovarian hormones have recently been found to be necessary for complete mammary development in most species of animals (Turner, 1932). The ovarian follicular hormone, theelin, characteristically induced a growth of the mammary duct system while the additional stimulation of the hormone of the corpus luteum was required for the complete development of the mammary alveoli.

The development of the mammary duct system of the normal female mouse occurs during the late pre-pubertal and the post-pubertal periods in virgin animals (Turner and Gomez, 1933; Cole, 1933; Gardner and Strong, 1935). The mammary alveoli were found to develop only during pregnancy or pseudopregrancy. The normal development of the female mammary glands has been duplicated experimentally by the administration of ovarian hormones.

Several series of mammary glands have been obtained from male mice bearing ovarian grafts and following ovarian hormone treatment over variable periods of time. The present report was planned to compare the mammary development induced by ovarian function in the male and the female body and that produced by the administration of the purified ovarian hormone.

Tamura (1927) placed ovaries under the tunica fibrosa of male mice. The grafts were made in mice 8 to 20 weeks of age and were recovered at autopsy 10 to 35 days later. The transplanted ovaries persisted during the period of observation in 27 of the animals. The effect of ovarian grafts upon the incidence of mammary tumors in male mice was studied by Murray (1928). The tumor incidence in males bearing ovarian grafts was similar to that observed in virgin females of the same strain. No control males developed tumors. The condition of the grafts or the degree of development of the mammary glands was not reported.

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[1]Read before the Nineteenth Annual Meeting of the Association for the Study of Internal Secretions, Atlantic City, N. J., June 11, 1935.

[2]National Research Council Fellow.

MATERIALS AND PROCEDURE

Ovarian transplants were made in 57 male mice. The ages at the time of grafting varied from 18 to 120 days, though the greater number were between 30 and 50 days. Animals were sacrificed at intervals between 7 and 415 days after the operation and the mammary glands, grafts, and other tissues were removed for study.

The ovaries were most frequently placed in the testes. Litter-mate sisters were used as donors[3]. The testes were exposed through a mid-abdominal incision. A small incision was made in the tunica albuginea and the ovary, transferred directly from the female, was placed among the seminiferous tubules. Some herniation of the tubules usually occurred. The entire ovary, ovarian capsule and a part of the Fallopian tube were occasionally implanted. In other mice the ovary alone was implanted. Sections of uterus were also placed in one testis of several mice.

The mammary glands were fixed, stained and examined as whole mounts. If areas were observed that appeared to warrant closer study they were removed and sectioned for observation at higher magnifications.

Theelin[4] in water solution was given to 64 male mice. The injections were started in animals at various ages and were continued for periods of 15 days to 11 months. The daily dosage varied from 2 to 8 rat units. A smaller series of mice were given an oil solution of folliculin benzoate[5]. All injections were made subcutaneously.

OBSERVATIONS

The mammary glands of the normal male mouse persist as rudimentary ducts in the subcutaneous connective tissue throughout life (Figs. 1 and 2). They undergo little, if any, growth after the weaning age. As male mice have no nipples there is no external indication of mammary stimulation as in the guinea pig. Because of their initial uniformly small size they critically portray the effects of the ovarian hormone.

Though the female mouse normally has 10 mammary glands, more than 8 mammary rudiments have never been observed in the males. The two caudal glands have not been observed in normal or theelin injected male mice and presumably never developed. In only a relatively small proportion of the male mice used were 8 glands found. Of the 30 mice listed in Table 1 only 9 were found to have all 8 glands. Seven glands were found in 5 mice, six in 7, five in 4, and four or less in 5. Some of the mammary rudiments might have been so small that they were overlooked. Some of the rudiments, though present, did not respond to theelin or to the ovarian grafts though other rudiments in the same animal had developed. The mammary glands of the third pair were most frequently missing.

[3]The mice were generously supplied by Dr. L. C. Strong. The letters used in referring to the mice are those used by Dr. Strong to designate the various strains in his colony.

[4]The theelin used in these investigations was kindly supplied by Parke, Davis & Co., through the courtesy of Dr. O. Kamm.

[5]The writer wishes to acknowledge the generosity of Dr. G. M. Smith, Research Associate in Anatomy, for obtaining the folliculin benzoate used in these experiments.

PLATE I

Figure 1. Silhouette drawings of 5 mammary rudiments obtained from a normal male mouse at 205 days of age. Enlarged 5.5 times.

Figure 2. Silhouette drawings of three control mammary rudiments obtained from a normal male mouse 85 days of age. Enlarged 5.5 times.

Figure 3. Photographs of the two glands of the second pair from mouse 50A removed 14 days after 2 ovaries had been implanted into the testes. The enlarged, densely staining ends of the ducts indicate a rapidly growing gland. Enlarged 3.4 times.

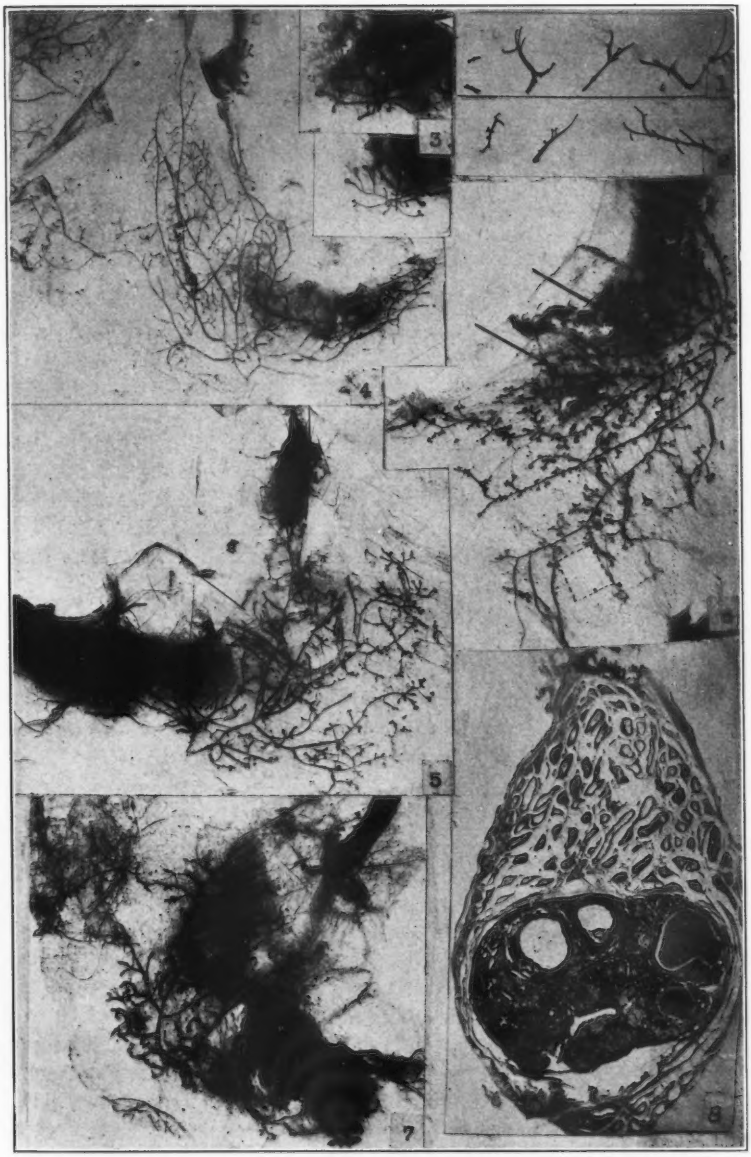
Figure 4. Photograph of one mammary gland of the second pair from mouse 16A removed 47 days after two ovaries had been grafted into the testes. The third pair of mammary glands in this mouse were still growing. Enlarged 3.4 times.

Figure 5. Photograph of a mammary gland of the second pair from mouse 57CBA removed 132 days after 2 ovaries had been implanted into the testes. One of the ovarian grafts is shown in Figure 9. Enlarged 3.4 times.

Figure 6. Photograph of a mammary gland of the second pair removed from mouse 21CBA 372 days after implanting two ovaries into the testes. The atypical overgrowth shown in Figure 10 was removed from this gland. Two other nodules are indicated by arrows. One of the grafts removed is shown in Figure 8. Enlarged 3.4 times.

Figure 7. Photograph of a mammary gland of the second pair removed from a mouse which had received 1080 rat units of theelin over a period of 320 days. The ducts were distended with a serous secretion. Enlarged 3.4 times.

Figure 8. A photograph of a testis bearing an ovarian graft 372 days (21CBA). Several large follicles and 2 blood follicles are seen. The remainder of the graft was made up of masses of interstitial cells and cords of epithelial cells. The seminiferous tubules had degenerated. Enlarged 15.5 times.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Male mice which had carried ovarian grafts for 14 days (46A and 50A) possessed actively growing mammary ducts. They were similar to those of animals receiving theelin for 15 days. All of the rudiments had not responded uniformly or simultaneously. The second pair of glands were undergoing rapid growth and had attained considerable size (Fig. 3), while the glands of the third or the lower thoracic pair and of the fourth or anterior inguinal pair showed no appreciable change. The first or anterior thoracic pair had started to develop. A similar gradient of response of the different mammary glands has been observed not only in the theelin-treated males but also in the females of some strains.

The mammary duct system of two male mice bearing ovaries for 22 and 39 days, respectively, were about one-half grown and still in an actively growing condition as indicated by the enlarged end buds of the ducts. Two active grafts were found in the testes of each animal. Three mice (45I, 39I, 26CHI) received daily injections of Antuitrin-S for ten days before autopsy. A total of 250, 150, and 100 rat units, respectively, were given. Though the mammary rudiments of mouse 45I had not developed, well-preserved ovarian tissue was found in each testis. The injection of Antuitrin-S had not induced the formation of normal corpora lutea though some thecal luteinization was observed. The grafts were otherwise comparable to those of the other mice. The mammary rudiments of the other two animals were likewise undeveloped. No ovarian tissue was observed at the site of implantation in the muscles of the back in mouse 26CHI. The ovaries in the testes of mouse 39I had become necrotic.

The second pair of mammary glands of the mouse 16A removed 47 days after implantation of the ovaries had reached their full size while (Fig. 4) the third pair of glands were still actively growing. After the grafts had been present for 59 days the glands had reached an extent of development not appreciably exceeded at later stages. The extent of the mammary duct system compared with that of normal virgin female mice at 60 days of age and of male mice that had received an optimal amount of theelin over a comparable period of time. Only the branching duct system had developed.

The extent of the mammary duct system was similar throughout the series of mice bearing ovarian grafts from 132 to 415 days (Figs. 5 and 6) with two exceptions in which a less extensive growth had been induced (5CBA and 48CBA). Atypical growths of lobules of alveoli were observed in the glands of 5 mice during this period (Fig. 10). One to several such lobules were observed in each mouse. Some of the lobules appeared to be actively secreting while others were inactive. These lobules grossly resembled those which develop uniformly throughout the entire gland under the influence of the corpus luteum. Similar localized overgrowths have been observed in the mammary glands of male mice that had received theelin for comparable periods of time.

Of the 57 ovarian implants made into the testes 9 were not recovered or had degenerated. In 4 testes no ovarian tissue was found. Two of these

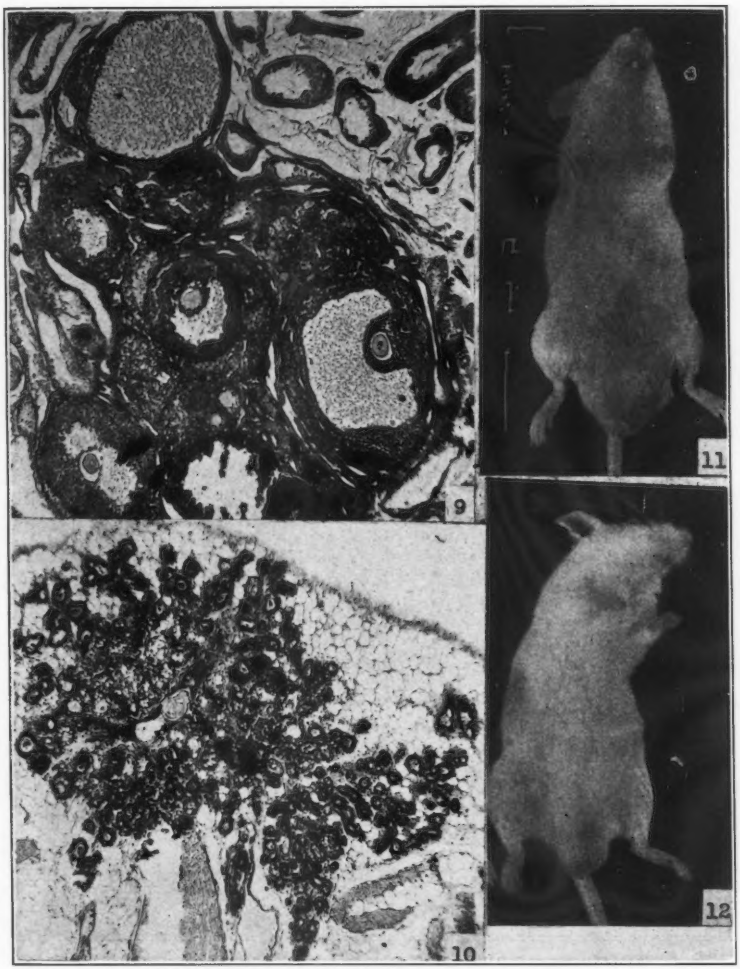

PLATE II

Figure 9. A section of the ovarian graft removed from mouse 57CBA, 132 days after grafting. The graft contained several large follicles. One blood follicle was present in the lower central section. Though the tubules near the graft show some damage, the greater part of the testes contained normal tubules. Enlarged 43 times.

Figure 10. One of the nodules removed from the mammary glands of mouse 21CBA. The area from which this nodule was removed is shown in Figure 6. The nodule consists of a clump of alveoli with vacuolated epithelial cells. The duct near the center of the group of alveoli contains a concretion-like mass of secretion. Enlarged 47 times.

Figure 11. Ventral view of a mouse which had received weekly injections of 500 international units of folliculin benzoate for 15 weeks. The large scrotal hernias developed 6 to 8 weeks after the injections were started. Upon autopsy a testis of normal size was found in each scrotal sac. In addition the slightly enlarged bladder extended into the left and the ceacum and a coil of intestine in the right sac. These hernias appeared uniformly in 6 mice so treated.

Figure 12. Ventral view of a mouse which had received daily injections of 10 rat units of theelin for 15 weeks. The scrotum was indistinguishable from that of normal male mice.

testes were removed from one mouse in which the mammary duct system was well developed (4CBA) so at least one of the ovaries must have persisted outside the testes. One testis in each of 3 mice had become entirely necrotic. The remaining testis in each animal contained a functioning graft. The ovarian tissue in both testes of one mouse (39I) had undergone degeneration.

Large and small follicles, cystic follicles, and atretic follicles were found in the grafted ovarian tissue (Figs. 8 and 9). Very few normal follicles were observed in some of the older grafts. They were composed largely of follicular cysts and interstitial elements. No corpora lutea were

TABLE I

THE PERSISTENCE OF OVARIAN GRAFTS IN MALE MICE AND THEIR EFFECTS UPON THE MAMMARY RUDIMENTS

Mouse Number	Age at Grafting	Age of Graft	Number of Grafts	Number of Glands Found	Condition* of Glands	Condition* of Grafts
	Days	Days				
46A	60	14	2	6	G	++
50A	39	14	2	8	G	++
3CBA	33	16	2	7	−	−−
34I	36	22	2	2	G	++
15CBA	31	39	2	5	G	++
45I	64	41	2	1	−	++
39I	45	42	2	4	−	−−
16A	30	47	2	7	D	++
24A	33	59	2	8	D	++
27CBA	34	59	2	8	D	++
42CBA	44	132	ov. ut.	8	D	++
57CBA	47	132	2	6	D	++
51CBA	45	135	2	6	D	−+
47CBA	66	138	2	4	D	++
44CBA	44	140	ov. ut.	5	D & N	++
33D	44	144	2	3	D	++
22CBA	120	176	1	5	D	++
31CBA	36	213	2	5	D	++
19CBA	30	264	2	8	D & N	+−
13CBA	29	313	2	6	D	++
5CBA	33	317	2	6	½D	+0
12CBA	29	342	2	8	D	+−
4CBA	33	364	2	7	D	−−?
21CBA	28	372	2	8	D & N	++
48CBA	66	372	2	6	D	++
16CBA	29	379	2	8	D & N	++
9CBA	32	385	2	6	D & N	++
10CBA	33	399	2	7	D	++
14CBA	30	400	2	7	D	++
6CBA	33	415	2	8	D	+−

*G Mammary glands growing.
D Duct system completely or nearly completely developed.
N Localized nodules of alveoli present.
+ Normal ovarian tissue observed.
− No ovarian tissue or degenerate tissue found in testes or graft sites.

observed. Sections of Fallopian tube were occasionally observed. The tubal epithelium was ciliated and well developed. Secretion was usually present in the lumen. The grafts of the sections of uterus were also well established.

The testes bearing the younger grafts contained normal seminiferous tubules except in the immediate vicinity of the implanted tissue. Several of the older grafts had largely replaced the tubules, particularly when large cysts had developed. Normal testicular tissue was present, however, in the testes of some of the older mice.

Ovarian tissue under the environmental influences of the male body thus induced a development of the mammary ducts system comparable to that observed in virgin females. The extensive development of mammary alveoli which Turner and Gomez (1934) have shown to require the hormone of corpus luteum was not observed, though a localized development of lobules of alveoli occurred in some mice.

The males treated with theelin or folliculin benzoate were divided into 3 groups. In the first group were 28 animals from 3 strains. From 2 to 8 rat units of water soluble theelin were given in one or two injections daily over a period of 15 days. The theelin originally contained 50 rat units per cubic centimeter, but was diluted with saline just before injection to contain 10 units per cubic centimeter. The mice varied in age from 94 to 346 days.

One injection of 2 rat units of theelin daily produced very slight or no mammary growth in 2 mice. When 2 rat units of theelin were given daily in two injections, a slight growth of the mammary ducts was induced in two of three treated mice. One or two injections of 4 rat units of hormone daily produced a relatively uniform mammary growth. Larger amounts of theelin produced similar effects.

These results indicated that two daily injections of the water soluble hormone were more effective than one injection daily, and that over two rat units per day were necessary to stimulate optimal mammary growth in male mice over 100 days of age. In this series the age factor was not of determinable significance. One rat unit of theelin produced optimal mammary duct growth in younger mice (Gardner, Diddle, Allen, and Strong, 1934). Some variation in response to the same amounts of theelin was observed in animals of the same strain. It was indicated that the glands of one strain responded less readily.

More extended periods of theelin treatment were made in a second series of 38 male mice (Table II). The resulting mammary glands were divided into 3 classes, depending upon the degree of response. The designation of ++ was used in reference to completely developed mammary duct systems; that is, the mammary glands of such animals were comparable to those of mature virgin females. A less extensive development of the mammary glands was designated as + and a failure of response as —. The

TABLE II

THE EFFECT OF VARYING AMOUNTS OF THEELIN OVER LONG PERIODS OF TIME UPON THE MAMMARY GLANDS OF MALE MICE

Number of Mice	Number of Injections Daily	R. U. Injected Daily	Days Injected	Condition of Glands Number of Mice in the Three Classes		
				++	+	−
6	1	2	15–68	0	0	6
11	2	3	55–309	8	3	0
21	2	4	60–292	12	9	0

++ Mammary glands showed a very extensive duct system.
+ Mammary glands showed a moderately developed duct system.
− Mammary glands did not respond.

periods of injection varied from 15 to 335 days for the different animals. As in the preceding group, 2 rat units of theelin daily were not effective. The mammary glands of all of the mice responded maximally or partially to 3 and 4 rat units daily (Fig. 7). The ducts were frequently distended with a clear secretion similar to that observed during late estrus in young mice. The mammary glands of 4 of the mice contained in addition to a well-developed duct system, one or more lobular areas of alveoli similar to those observed in the mice bearing ovarian grafts.

In addition, a small series of male mice received injections of folliculin benzoate dissolved in oil. The mammary glands of 5 animals receiving weekly injections of 100 to 500 international units over periods of 3 to 15 weeks have been examined. The injection of large amounts of hormone did not accelerate or extend mammary growth. Other animals are still being treated. The mice receiving weekly injections of 500 rat units of the folliculin benzoate, when injected from the 4th week of life, all developed large scrotal hernias after 6 to 8 weeks of treatment.

DISCUSSION

Since the investigations of Steinach (1912) numerous investigators have dealt with the effect of ovarian grafts in the male body. Most of the investigations have been conducted on guinea pigs. Smelser (1933) reported on the influence of ovarian grafts on the mammary glands of male and female guinea pigs. He found that 95 per cent of the grafts failed to induce mammary growth over a period of 4 to 6 months when placed in normal males. If, however, the animals were made cryptorchid or castrated, the mammary glands of 75 to 80 per cent responded. The presence of normal functioning testes appeared to inhibit, though indirectly, the hormone-producing capacities of the ovarian grafts.

Though the method used in making the grafts in the mouse may not be considered to offer critical information on the functional activity of both testes and ovaries in the male body, it was indicated that the male mouse may simultaneously support both functional testes and ovaries. Active ovarian grafts, normal seminiferous tubules, and well-developed seminal vesicles and mammary duct systems have been observed in males bearing ovarian grafts in numerous instances. In a number of animals, however, the male accessories had regressed and the testes contained largely grafted ovarian tissue. In only one instance were well-preserved ovarian grafts found in which no mammary gland growth had been induced. One mouse with untouched testes, bearing a subcutaneous ovarian implant, had actively growing mammary glands. It might be assumed that, whereas the pituitary gonadotropic hormone available to the normal male guinea pig was below the ovarian graft threshold, that available in the male mouse was above the threshold of response of the graft.

Engle (1927-28) found that the administration of anterior pituitaries stimulated ovarian tissue in the testes of rats and increased the number of successful grafts. The stimulated grafts induced a marked growth of the

mammary glands. The extent of mammary hypertrophy observed by Engle (1927-28) in the rats appeared to exceed that observed in the mice reported here. The comparison, however, is not justified as the pituitary therapy used greatly stimulated the grafts in the rats.

The attempt to compare the mammary gland development of male mice bearing ovarian grafts and of males receiving varying amounts of theelin was complicated by the variations of growth observed even within the same inbred strains under uniform experimental conditions and by the difficulty encountered in accurately estimating the relative extent of mammary development. The extent of mammary gland development was more uniform in the graft-bearing mice than in the theelin-treated mice. Of the 23 males bearing ovarian grafts for 47 days or more, only 2 (5CBA and 48CBA, Table I) had small mammary duct systems. Of the 32 mice receiving 3 or 4 rat units of theelin daily for more than 55 days, 12 had small duct systems.

The extent of development of the mammary duct systems of most of the male mice bearing ovarian grafts or receiving theelin injections was comparable to that of mature virgin females. Unlike the guinea pig (Smelser, 1933), the ovarian tissue in the male was not capable of stimulating more extensive mammary development than observed in normal females.

The localized lobules of alveoli had been observed in the mammary glands of 3 mice from one strain (C_3H) following the injection of theelin for 135 days or more (Gardner, Diddle, Allen, and Strong, 1934). The females of this strain were very susceptible to mammary cancer. Similar mammary nodules (Fig. 10) were observed in the mammary glands of graft bearing male mice from the CBA strain (Dr. Strong) which are very resistant to mammary adenocarcinoma. The mammary glands of virgin and multiparous female mice from the same strains have been found to contain these nodules of alveoli in otherwise involuted glands (Gardner and Strong, unpublished).

The variations in rate of growth of the different glands in the same animal were observed not only in the normally developing glands of females, but also in those experimentally developed. Why some of the male rudiments should not respond or respond more slowly is not known. The second pair of glands may possibly receive a better blood supply and hence more mammary growth-stimulating hormone. Some of the rudiments which remain undeveloped even in theelin-treated or graft-bearing animals must be quite insensitive to the usual growth-stimulating factor or not accessible to it.

The mammary glands of the small number of animals which have received 100 to 500 international units of hormone weekly in the form of folliculin benzoate in oil solution developed at the same rate as those receiving the water-soluble theelin. Six mice receiving the larger dose of folliculin benzoate starting at 4 weeks of age all developed large scrotal hernias after 6 to 8 weeks of treatment (Fig. 11). Hernias were also observed in 2 mice

bearing grafts. None was observed in the theelin-treated mice. The development of scrotal hernias has been observed previously by Burrows and Kennaway (1934).

Mammary tumors were observed in the male mice from tumor susceptible strains after they had received ovarian grafts (Murray, 1928). Lacassange (1932) has made similar observations following the injection of large amounts of folliculin benzoate. Though all but 3 of the theelin-treated mice reported in the present paper were from tumor susceptible strains, no mammary tumors had developed. All of the animals of tumor age in the ovarian-graft series were from a tumor resistant strain. The investigations are being continued for the purpose of determining the possible relationship of the stimulants of normal mammary growth to abnormal growths.

SUMMARY

Ovarian grafts into the testes of mice function in the stimulation of mammary growth in a manner comparable to the ovaries in the normal female mouse. The action of ovarian grafts in the stimulation of mammary glands can be duplicated by the continued injection of 3 to 4 rat units of theelin daily in two injections, although the grafts produce more consistently uniform effects.

The mammary rudiments of the male mice stimulated by the ovarian grafts and theelin injections develop into extensive duct systems comparable to the mammary development observed in normal virgin female mice. Localized lobules of alveolar tissue have been observed along the mammary ducts of animals bearing ovarian grafts and of animals receiving theelin injections. These lobules appeared in animals from both tumor-susceptible and tumor-resistant strains.

The mammary glands of male mice receiving weekly injections of 100 to 500 international units of folliculin benzoate in oil developed at approximately the same rate and to the same extent as the glands of animals receiving theelin. Scrotal hernias were observed in the mice receiving the larger dosage.

All of the mammary rudiments of many male mice did not respond to theelin or ovarian stimulation. The second pair of glands usually responded most readily.

The presence of functional ovarian grafts in the testes of the mice was not incompatible with the normal endocrine function of the testicle as judged by the maintenance of the male accessory genital organs.

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CERTAIN FACTORS AFFECTING THE CONSTANCY OF IMPEDANCE ANGLE

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In 1933, Brazier (1), (2) described a technique for determining thyroid function and, more particularly, hyperfunction of this gland by measurement of an electrical property of the body called the impedance angle.

The impedance angle is the complement of the power factor or phase angle currently used in electrical engineering to determine to what extent the current and the voltage in an alternating current circuit are out of phase with one another.

For the human body, the phase angle is expressed by the following equation:

Tangent phase angle=2π (resistance X capacity X frequency).

The impedance angle= $\pi/2$—the phase angle.

Impedance angle values are expressed in Brazier units obtained by subtracting the normal phase angle values for males and females, 0.138 and 0.110, respectively, from the phase angle value found and multiplying by —1000.

Thus a male giving a phase angle of 0.157 has an impedance angle of $(0.157 - 0.138)\ (-1000) = -19$ Brazier units.

The normal limits for females are +10 to —11 units and for males +12 to —13.

Single determinations may be made to an accuracy of 1 per cent but may vary ± 2.3 per cent over a period of time. They are not affected, according to Brazier, by body activity, meals, mental state or menstruation. This makes it possible to run tests without any of the preparations necessary in basal metabolism work.

It is our purpose herein to report on two factors, one instrumental and the other physiological, capable of affecting the constancy of impedance angle.

Instrumental Factor. The frequency being known, it is merely necessary to determine the resistance and the capacity to calculate the phase angle. In Brazier's original technique, this was done by means of a Wheatstone bridge constructed to permit both resistance and capacity to be measured. However, these two values cannot be simultaneously determined. The bridge is first adjusted to take care of the resistance (impedance) of the subject and, when this has been accomplished, a second series of operations are effected on the bridge to measure the capacity. The subject under test meanwhile immerses both arms above the level of the elbows in a pair of arm baths containing 10 liters of normal saline and current is led from the bridge terminals to the arm baths by means of a pair of cables connected to lead electrodes dipping into the saline. Strictly speaking,

a Wheatstone bridge measures impedance rather than resistance, but since the impedance and the resistance of the human body are substantially equal, in order to avoid confusion of the terms impedance and impedance angle, the term resistance will be used throughout instead of impedance.

In attempting to make impedance angle measurements in this way for the first time, it was observed that, after the bridge had been adjusted for resistance, if the subject being measured contracted his biceps, the adjustment for resistance on the bridge took a different value. Further tests showed that various movements of the shoulders and the head modified the value of resistance as determined on the bridge. This indicated that the resistance values were dependent upon the state of tension or relaxation of certain skeletal muscles and that impedance angle determinations on a Wheatstone bridge were subject to error from this cause. The change in resistance due to contraction of the biceps, raising the shoulders, flexing or extending the head varies from 0.5 to 2 per cent. However, it may be shown mathematically that, if the resistance balanced out on a Wheatstone bridge varies as much as 1 per cent, the error in phase angle due to the effect on the subsequent capacity determination may rise to 10 per cent.

In order to check the phase angle values obtained with the Wheatstone bridge, a phase meter of a new type designed by one of us (S. B.) was used and it was noted that the phase angle measurements made with this latter instrument remained invariable irrespective of the state of tension or relaxation of the subject. This phase meter differs from a Wheatstone bridge in its operation in that successive adjustments for resistance and capacity are unnecessary, the combined effect of the latter on the phase angle being simultaneously indicated.

Inasmuch as the phase angle is a function of the product of the resistance by the capacity, the constancy of phase angle in this latter type of instrument indicated that any instantaneous increase in body resistance as a result of change in muscular tension was compensated for by a corresponding decrease in capacity and vice versa. Were a Wheatstone bridge used, and should the muscular tension of the subject have changed after the resistance adjustment had been made, the capacity value subsequently determined would correspond to the changed, and not to the original, resistance. Moreover, since phase angle determinations with the phase meter could be effected in a fraction of the time necessary for manipulating a Wheatstone bridge, the phase meter* was adopted in all subsequent work.

The phase meter is shown in Figure 1. (See next page.)

Physiological Factor. In Brazier's original article (1) it was stated that the impedance angle remains constant from day to day for women over the menstrual period.

While this appears to be true for normal women, it has been found that it does not apply in certain pituitary conditions.

*This phase meter has been used at the Brooklyn Jewish Hospital in a comparative study of I. A. and B. M. R., covering more than 250 cases. The results of this investigation, recently completed, will be published in a separate paper.

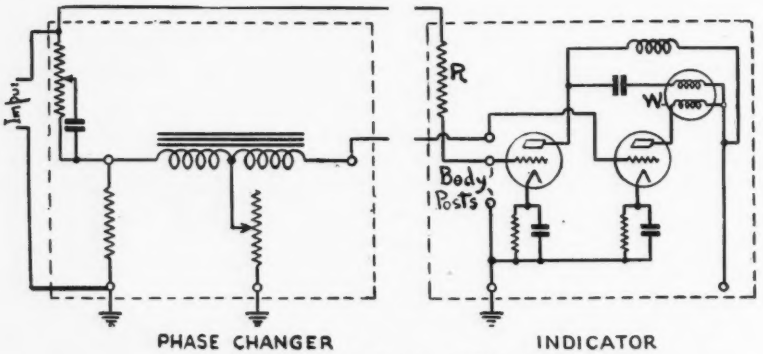

Figure 1. Wiring Diagram of Phase Meter.

It is composed of (1) an oscillator capable of transforming 60 cycle into 15,000 cycle current, (2) a phase changer and (3) a phase indicating unit utilizing either a wattmeter or a cathode ray tube as a null instrument. The oscillator is not shown and may be of any type yielding a minimum of harmonics. The phase changer is represented on the left of Figure 1 and is composed of a center-tap transformer connected to a variable resistance in the manner indicated. Its effect is to provide a variable inductance compensating for the body capacity. The phase indicator is shown at the right of this figure and its two wattmeter coils (W) are fitted with triode tubes acting to isolate the wattmeter. The phase angle indications may be amplified if desired. A large resistance (R) (20,000 ohms) is connected in series with the body terminals to render the effect of different body resistances on the phase angle negligible. Determinations may be made in two minutes with this instrument and to an accuracy of 1 per cent.

In operation, a pure resistance is first inserted across the body terminals and the phase changer and null instrument are brought to a zero reading. By means of a switch, the subject to be measured is substituted for the pure resistance and the phase changer is again adjusted until the null instrument once again reads zero. The phase changer is provided with a scale calibrated in terms of phase angle and the readings thereon directly indicate the values sought. If it be desired to measure the body resistance of the subject, a rectifier voltmeter calibrated in ohms is thrown across the body terminals and its indications are taken as proportional to the body resistance or impedance.

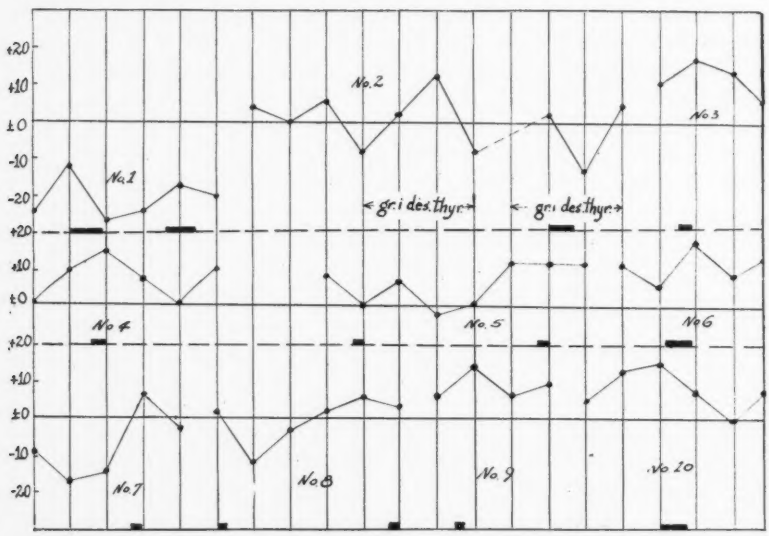

Figure 2. Variation in I. A. as a function of time. Ordinates in Brazier units. Abscissae in weeks. Menstrual periods are shown by a black bar.

Case No. 2 began taking anterior pituitary powder, gr. XX daily, three months before the test began and continued throughout. She received desiccated thyroid, gr. i daily in addition as indicated. The remaining subjects took no medication of any kind.

In Figure 2 impedance angle curves are shown in one case of pituitary dwarfism (subject No. 1) and nine unselected cases diagnosed clinically as hypopituitarism. Measurements were made weekly. Subject No. 1 was an unmarried woman, 23 years of age, 137 cm. in height and weighing 38 kilograms. Her basal metabolic rate was +12 per cent, while the impedance angle varied between —12 and —24. The hypopituitary subjects were all obese women reporting irregular menses and showing varying moderate degrees of hirsutism.

COMMENT

The fact that the alternating current resistance of the body measured through the skin changes with muscular tension while the product of the resistance by the capacity remains constant under these conditions suggests that, at a frequency of 15,000 cycles, the skin either exerts a constant effect on the impedance angle or does not come into play at all. Brazier (1) claims to have shown that above 9000 cycles the impedance angle measures the effect of structures lying below the skin. This she concluded from the fact that the body resistance measured with the arms immersed remained substantially the same after the skin had been short-circuited by needles penetrating into the underlying muscular tissues. It may be noted that the resistance to a needle, particularly at the point, is high enough to make it questionable whether a true, short-circuiting effect is obtained under these conditions.

Brazier and Grant (3) have reported impedance angles in an individual of +7, —21 and —14 on different days. No diagnosis was given, nor was any cause assigned for these variations. These same workers also reported a single case in which the impedance angle decreased under thyroid medication. Subject No. 2 is a second case of this type, the impedance angle curve showing two distinct descending portions during the period in which desiccated thyroid was given. It will be noted that, although this subject was taking 20 grains of anterior pituitary powder daily, her curve does not differ materially from those who took none.

The cases herein reported indicate that impedance angle is not only subject to variation in special cases, but is capable of being influenced by other than thyroid factors. In the single case of pituitary dwarfism with values fluctuating between —12 and —24, there was no evidence of thyroid deficiency, the basal metabolic rate being +12 per cent. It has been shown that the proportion of growth hormone in the pituitary glands of adult cattle is as great as in those of young calves (4). If it be assumed that this subject was deficient in growth hormone, the low impedance angle might be due to this cause. Study of the effect of pituitary growth hormone on impedance angle is now in progress. It may be noted that this fraction, according to Thompson and his co-workers (5), is capable of increasing the basal metabolic rate.

In 7 of the 9 cases of hypopituitarism (all but cases 2 and 5), the maximum impedance angle occurred at or near the menstrual period. Fur-

ther work is being carried on to determine whether or not a gonadal pituitary factor is here involved.

SUMMARY

1. It has been shown that the body resistance measured with an alternating current of 15,000 cycles frequency varies with muscular tension and that impedance angle values obtained with a Wheatstone bridge are subject to error if the body resistance is determined in one state of muscular tension and the capacity in another.

2. A phase meter is described giving constant phase angle values irrespective of changes in muscular tension during test.

3. The impedance angle in one case of pituitary dwarfism and in nine unselected cases presenting clinical evidence of pituitary deficiency, has been shown to follow a fluctuating course.

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EXPERIMENTAL STUDIES OF THE ANTERIOR PITUITARY. III. OBSERVATIONS ON THE PERSISTENCE OF HYPOPHYSEAL TRANSPLANTS IN THE ANTERIOR EYE CHAMBER

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Despite the extensive literature dealing with experimental work on the mammalian hypophysis the possibility of semi-permanent transplantation and its bearing upon certain aspects of endocrine physiology has been strangely neglected. Wide use has been made of pituitary substance, as fresh minced tissue or in extract form, and a considerable number of extremely pertinent observations have accrued as a result. Certain problems arise, however, the key to which apparently will not be obtained other than by the classical method of transplantation. A feasible technique would be easily adaptable to crucial experiments which should establish beyond equivocation various problems of a fundamental nature, evidence concerning which is still obscure or, at best, conflicting in nature; such, for example, as the necessity of nervous connections for the maintenance of normal pituitary functions. With respect to the other well-established glands of the endocrine system, freedom from dependence upon nervous pathways has long been known; it has been more or less tacitly assumed, however, in the case of the hypophysis, so closely associated with the brain and serving so striking a rôle in the animal economy, that nervous connections with the latter organ control in some manner its normal mode of action.

The present communication is concerned, therefore, with observations relative to the survival and persistence of homoioplastic pituitary tissue when engrafted in the intact animal in such a manner that its persistence may be observed readily and any changes noted from day to day. In view of the striking success obtained with other tissues when implanted into the anterior eye chamber (Markee, 1932; Goodman, 1934) this site was employed for engrafting material, with results which amply justified its selection.*

EXPERIMENTAL PROCEDURE

Adult guinea pigs and rabbits, purchased from a local dealer, were used as experimental animals.† In each instance one animal was sacrificed for glandular material. The gland was bisected and one-half quickly implanted into each eye of an anesthetized experimental animal. In this routine each eye in turn was bathed with Dakin's solution and gentle pressure

*Preliminary data recently were reported before the American Association of Anatomists, April, 1935.

†Siblings were not employed in this work, and it seems probable that even more striking success should be obtained with such animals.

PLATE I

All 7 figures are photomicrographs of the pars anterior of the rabbit pituitary, stained with haematoxylin and eosin.

Figure 1. Normal gland showing cellular arrangement (X 80).

Figure 2. Gland recovered from the anterior chamber of the eye 16 days after implantation, showing cellular arrangement essentially the same as in the normal (X 80).

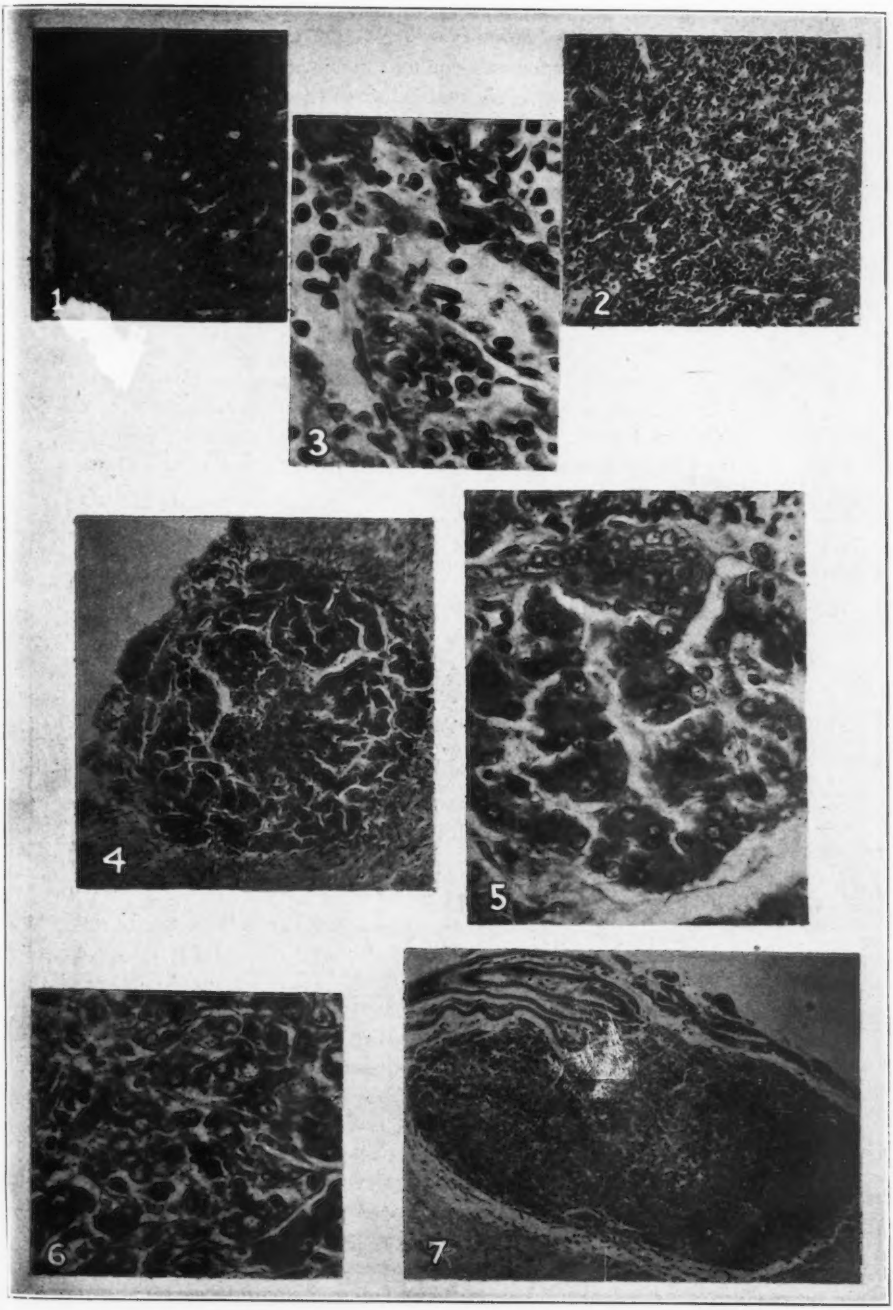
Figure 3. A small region of 16-day implant near the periphery showing the presence of scattered lymphocytes (X 450).

Figure 4. Gland recovered after 25 days' implantation. Note the loss of compactness (X 200).

Figure 5. Same as Figure 4 (X 400).

Figure 6. Same as Figure 7, showing the definite nest formation (X 400).

Figure 7. Tissue recovered after 31 days' implantation (X 200).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applied to extrude the globe. The conjunctiva was grasped with tissue ("mouse-toothed") forceps and by means of a Graefe's linear cataract knife an incision of 3 to 4 mm. was made in the corneo-scleral junction. A pair of Bloemer's cup-shaped cilia forceps was utilized for insinuating the tissue into the pupillary area. Intra-ocular pressure at first usually flattened the implanted material, which occasionally fragmented somewhat. Because of the pultaceous character of the glandular material spoon-shaped forceps were found particularly invaluable for making the eye implants. Occasionally some fluid was lost, for which there was usually a rapid compensation. No sutures were necessary and healing occurred without incident. For a period of 10 to 12 days the anterior chambers remained cloudy, after which they cleared rapidly and the implants, generally attached to the iris, could be observed with striking clarity.

Animals were sacrificed at intervals following transplantation, the eyeballs were fixed in warm Zenker-formol-osmic, embedded in paraffin or celloidin-paraffin, sectioned, and stained with Delafield's hematoxylin and eosin. Successfully recovered material ranged in age from 16 to 114 days, the latter being the longest experimental period.

HISTOLOGICAL OBSERVATIONS

It should be pointed out that in the anterior pituitary of the normal guinea pig the demarcation of the nests of cells is made prominent by the presence of well-defined sinuses which break up this portion of the gland. Areas may be found, however (Fig. 8), in which a less prominent nesting occurs. Moreover, in the pars anterior of the normal rabbit the cell groups are less prominent (Fig. 1) and, unless the gland sinuses are well-filled with blood elements, the nesting arrangement becomes apparent only upon close examination. These general observations are of importance in the study of implanted anterior pituitary tissue, since to disregard them may lead to misinterpretation of the condition of the grafts.

Rabbit Pars Anterior Material (Plate I). Implants were recovered from the anterior eye chamber of the rabbit at intervals of 16, 25, and 31 days. The 16-day implants showed no apparent changes from the normal. The cells stained normally, an occasional mitotic figure could be observed, and the nesting arrangement was undisturbed. There was no evidence of vascularization. Erythrocytes, found sparsely distributed in the sinuses, appeared slightly rounded but were normal in their staining reaction. A few lymphocytes could be observed grouped round the periphery of the implants and in some of the blood spaces (Figs. 2, 3). The 25-day implants showed a loss of compactness and the spaces separating the nests of cells were, in consequence, definitely more prominent. Here again the cells appeared normal. Mitotic figures could be observed in most fields. There was no evidence of vascularization and the occasional groups of red cells in the interspaces appeared to have lost their concavity, although they stained normally (Figs. 4 and 5). The 31-day implants appeared well-defined and no less compact than those of 25 days. The cell nests were prominent, con-

sisting of normally staining cells fairly well differentiated, with nuclei varying from the compact to the vesicular. A good many mitotic figures could be observed throughout the implanted material. There was some indication of leucocytic infiltration, especially round the periphery (Figs. 6 and 7).

Guinea Pig Pars Anterior Implants (Plate II). Implants were recovered at intervals of 36, 91 and 114 days. The 36-day implants showed clear-cut nesting arrangements consisting in well-defined and normally differentiated anterior pituitary cells. Occasional mitotic figures were fairly prominent. There was no evidence of vascularization and the occasional erythrocytes found in the sinuses appeared to have lost their concavities but were normal in their staining reactions (Fig. 10). Many groups of leucocytes, lymphocytes for the most part, were observed round the periphery of the grafts (Fig. 12). Occasionally the implant consisted of more than one part, due, no doubt, to fragmentation during the process of grafting.

The pituitary tissue of pars anterior grafts examined after 91 days presented an extremely interesting picture. The cell nests could be easily distinguished by virtue of the endothelial borders. The interspaces had become less prominent, with only occasional blood elements present. A great many prominent mitotic figures were found in all fields (Figs. 11 and 16). The border was sharp in all sections and gave no indication of being broken by any cellular infiltration from the surrounding media. At some points along the periphery groups of leucocytes could be seen. There was no evidence of vascularization (Fig. 13).

Anterior pituitary tissue sectioned after 114 days' retention in the anterior eye chamber showed a sharply delimited border (Fig. 14). The cells making up the implant were well-defined and the majority of areas showed typical nesting arrangement (Fig. 15). The interspaces for the most part had disappeared but their positions could be easily ascertained by the endothelial cells of their linings. Mitotic figures could be found in many fields. Occasional red blood cells found between the cells appeared to have lost their concavity, and were attenuate, due, possibly, to intercellular pressure.

DISCUSSION

Cushing and his collaborators (1909) were perhaps the first to make serious attempts at transplanting pituitary tissue. In their experiments, which at that time were devoted to finding a means of prolonging the life span of hypophysectomized dogs, auto-transplants of freshly removed tissue were made variously into rectus muscle, bone marrow, and cerebral cortex. At best, however, they were able to maintain their animals only from 18 to, in one case, 26 days, and histological examination of the grafts showed some evidence of apparently active anterior lobe tissue in peripheral areas. For the most part, however, their implants were unsuccessful and glandular material was not recovered. In 1932 Hohlweg and Junkmann

PLATE II

All 9 figures are photomicrographs of the pars anterior of the guinea pig pituitary, stained with haematoxylin and eosin.

Figure 8. Normal gland showing a region of well defined cell nests adjoining a more compact area in which the cell groups are less clearly outlined (X 80).

Figure 9. Normal gland showing an area near the periphery in which the characteristic and well defined cell nests are shown bounded by the endothelial lining of the capillaries (X 240).

Figure 10. An area from a gland recovered after 36 days' implantation showing several of the rounded red blood cells in a capillary (X 450).

Figure 11. A region from an implant 91 days old showing many mitotic figures (X 400).

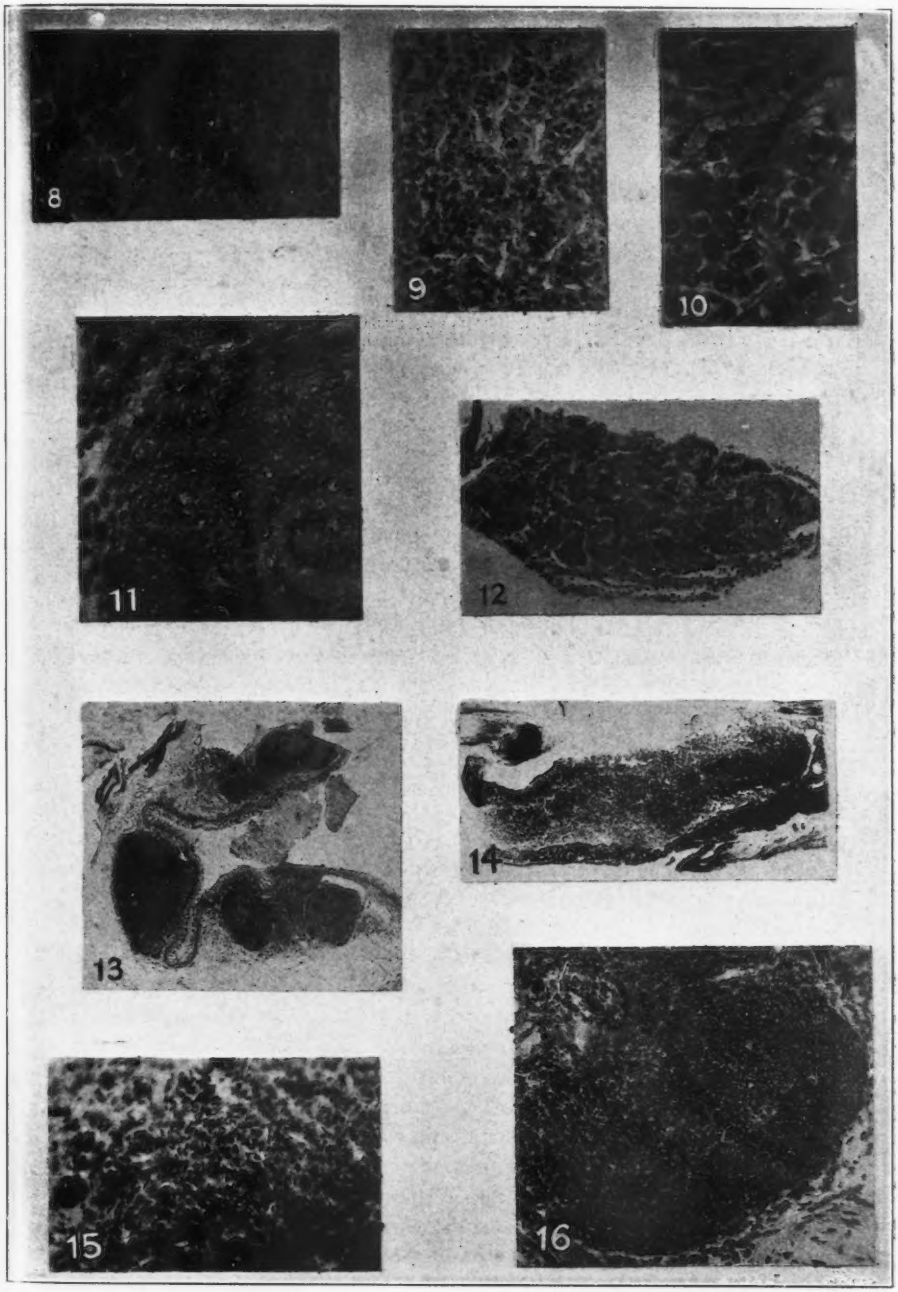
Figure 12. Gland tissue recovered after 36 days' implantation showing nesting arrangement of the cells with a great many nuclei in the compact phase and heavily stained. Many lymphocytes may be seen arranged around the periphery of the tissue (X 80).

Figure 13. A 91-day-old implant showing 4 separate pieces as a result of fragmentation during implantation (X 40).

Figure 14. Gland tissue after 114 days' implantation showing a definite increase in compactness (X 40).

Figure 15. Same as Figure 14. Cell nests may be seen outlined by endothelial cells (X 200).

Figure 16. Same as Figures 11 and 13, showing a great many mitotic figures (X 240).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implanted rat pituitary into the kidneys of intact animals which subsequently were castrated. Upon recovery of the grafted tissue, one month later, no castration cells were apparent whereas the hosts' pituitaries revealed characteristic structural changes. No histological evidence was offered, however, and their report is rather unconvincing. We have recently reported (1935) that when homoiotransplants were made into the eye chamber, both of rabbits and guinea pigs, differentiation persisted for at least 5 to 6 weeks—a period which since then has been extended to over four months. Hill (1935), in a simultaneous report based upon subcutaneous heteroplastic transplantation of fresh pituitary tissue in immature female mice, was successful in recovering tissue upon subsequent sacrifice, although the length of retention was not stated. More recently Gardner and Hill (1935) have presented evidence that, in the mouse, intratesticular implants of pituitary substance will persist for at least as long as 12 weeks. There was no evidence of mitotic activity. In the present report it is shown that homoioplastic transplants of anterior lobe into the eyes will persist, retain their histological differentiation (i.e., normal nesting arrangement and staining reaction), and show evidences of hyperplasia, as revealed by the presence of mitotic figures, for periods ranging up to 4 months—the maximum time allowed our experimental animals.

There are several points of interest in connection with these observations. In the first place it is evident that the anterior eye chamber, filled with a nutrient fluid in which, presumably, a transplant is subjected to equalized pressure on all sides, is an excellent medium for transplantation experiments of this nature. Moreover, the actual technique of transplantation is exceedingly simple; incidence of infection, with ordinary precautions, is negligible, and—a factor of prime importance—the persistence and gross characteristics of the grafts can be observed directly.

The question of possible blood supply to the transplants is rather a puzzling one. Careful study of serial sections has revealed no instance of an acquired blood supply; in fact, as pointed out elsewhere, the usual large sinuses of the pituitary material were narrowed or, in some instances, occluded altogether, probably because of the considerable intra-ocular pressure. Yet the cells of central areas appeared quite as normal as those of the periphery. These findings are perplexing in face of the fact that an oxygen deficiency exists in the intra-ocular fluids as compared with serum (Duke-Elder, 1927a). A possible explanation may be based upon the fact that the intra-ocular fluid has been shown to be a dialysate in equilibrium with the capillary fluids and that the "primary metabolic interchange" causes continual renewal of the intra-ocular fluid throughout all the vascularized tissues of the eye, causing fresh materials to be added and products of metabolism to be eliminated. Superimposed upon this is a pressure circulation, to which may be added also the convection currents of the thermal circulation of the fluids in the anterior chamber of the eye (Duke-Elder, 1927b and 1927c). These combined factors may be assumed to cause suffi-

cient bathing of the implants to control their metabolism, carrying off any waste products and, it seems likely, elaborated hormonal materials.

The finding of red blood cells in the grafts as long as 4 months after transplantation is of interest in connection with the possible longevity of these elements. From evidence obtained so far it is apparent that they have survived since the time of operation, and it remains to be ascertained actually how long they will retain their integrity under such unusual circumstances. In addition, it would be interesting to determine the kinetics involved in the loss of the concavities in these retained erythrocytes, especially in view of the analysis of the aqueous humor offered by Duke-Elder (1927a). His data reveal an osmotic pressure of 0.297 m., calculated by the freezing point depression method, on the basis that the presence of 0.1 gm. molecule of solute lowers the freezing point of water by —0.186° C. This would indicate a condition approaching isotonicity.

SUMMARY

A simple and effective technique is described for transplantation of the mammalian pituitary into the anterior eye chamber, a site shown to be an excellent one for the persistence of engrafted material.

Homoioplastic transplants of anterior lobe will persist in the eye chamber of rabbits and guinea pigs for periods of at least 4 months, during which time they retain their histological identity and may undergo some degree of hyperplasia. There is no evidence of established vascular connections, and it appears that such grafts obtain their nutriment from the surrounding fluid of the eye chamber.

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THE LAURENCE-MOON-BIEDL SYNDROME*

REPORT OF THREE CASES

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Since this syndrome was first described by Laurence and Moon in 1866 and later by Biedl in 1922, almost a hundred cases have been reported in the world's literature. Reilly and Lisser (1), in 1932, made an excellent survey and summary of the literature and concluded that the syndrome consists of six cardinal symptoms: obesity, mental deficiency, genital dystrophy, polydactylism, retinitis pigmentosa, familial occurrence.

Many other symptoms were reported by numerous authors such as deafness, syndactylism, atresia ani, nystagmus, etc. Some of these may have replaced one of the above mentioned cardinal symptoms. The symptoms are most probably caused by some one single cerebral defect which is hereditary in nature, occurring in families. It is conceivable that this defect may be inherited by siblings in different degree, with the subsequent absence or lack of prominence of one or more symptoms.

We are reporting three brothers who have inherited the syndrome, but each to a different degree. Not one of them has all the six symptoms, yet one of them would qualify if obesity and genital dystrophy were grouped under the heading of "pituitary dysfunction." The combination of obesity and genital dystrophy, mentioned in the cardinal symptoms, is the type recognized as Fröhlich's Syndrome, which is thought to be a disturbance of both the anterior and posterior lobes of the pituitary gland. If we accept the hypothesis put forward by others that it is a hypofunction of the anterior lobe alone, is it not possible that we may also have a short, obese individual, with a feminine distribution of the pubic hair and knock-knees? This would be a pituitary dysfunction different only in the degree of involvement.

Our three boys all have polydactylism and mental deficiency. Two have the Fröhlich type of pituitary dystrophy, while the third is short,

*Read before the Nineteenth Annual Meeting of the Association for the Study of Internal Secretions, Atlantic City, N. J., June 10, 1935.

obese and with feminine distribution of hair and fat. The familial aspect is satisfied and a paternal granduncle is said to have had polydactylism. The two boys with the Fröhlich Syndrome have a high grade of myopia, while the third boy is the only one with retinitis pigmentosa. There is no history of consanguinity present. The family is an interesting one and its history is given in detail.

The father was born in Italy, is a laborer, aged 47, and illiterate. He came to America at the age of 22. He is a short, obese man of low mentality, is a hard worker, but has been on "relief" for the past four years. He comes of a virile family and an uncle is said to have had polydactylism. He is a moderate drinker, is in excellent health and a blood Wasserman test gave negative findings.

The mother was born in Italy, is a housewife, aged 41, and illiterate. She came to America at an early age, married when 15 years old and soon began a series of pregnancies eventually becoming pregnant simultaneously with her married daughters. She is a short obese individual with a recognizable growth of hair about the face. She is a domineering sort and is the "boss" of the house. She feels that the community owes her a living and is known to every social organization in her county. She is not of the begging sort and receives charity as a favor to the contributor.

There are thirteen children, four boys and nine girls, as follows: Angelo, born in 1908; died in 1928, following an operation for appendicitis; Carmel, born in 1909, living, married, has had two sets of twins and is pregnant again; Irene, born in 1911, died in 1912 of "worms"; Mary Anne, born in 1912, died at birth; Rose, born in 1915, living and married to a "German" who doesn't believe in children; Rocco, born in 1917, living and has acquired syphilis (1933), for which he is being treated; John, born in 1919, will be described later in detail; Lena, born in 1920, died in 1922 of "worms"; Mary, born in 1922, ran away with a married man in 1934 and developed a bilateral salpingitis, has a heavy torso, is large for her age and is of moron intelligence; Dominic, born in 1925, and Leonard, born in 1927, will be described later in detail; Angelino, born in 1928, is living and just entered school; Lucille, born in 1931, is a small, chubby, beautiful child.

The three boys with the suggestive symptoms of Laurence-Moon-Biedl syndrome will now be described in detail.

Case 1. John was born in 1919, with normal delivery, walked at 2½ years, talked at 1½ years. Dentition, bladder and bowel control developed at the usual age. At the time of the physical examination (4-16-35) he was 58 inches tall (min. for age, 61) and weighed 134 lbs. (max. for age, 122). Vision was difficult to ascertain because of the low mental level, but the pupils were equal and regular and reacted normally. There was no strabismus but retinitis pigmentosa was present. Chronic otitis media was noted in the right ear and calcareous deposits on the left ear drum. The teeth were in good repair and there was a high arched palate. The tonsils were enlarged but not septic. An anterior cervical adenopathy was present. Examination of the heart, lungs and abdomen gave negative findings. The genitalia were normal in size and both testes were descended. Pubic hair was abundant. He had six fingers on the right hand and six toes on each foot. The body configuration was feminine—large breasts, pendulant abdomen, knock-knees and much fat about the buttocks and thighs. He had a double chin, hair on the upper lip, on the cheeks and underarms. The secondary sexual characteristics appeared to be normal for age. The blood pressure was 118/78. The circumference of the head was 21½ in.

(21.9 average for age), circumference of the chest 33¼ in. (31.0 average for age), of the abdomen 33¼ in. (26.8 average for age). His span was 58 (min. for age, 62.3). The lower measurement was 27½ in. (min. for age, 30.5), and the upper measurement 30½ (min. 29.5, max. 32.5). The measurement above thighs was 38, at level of trochanters. The width at the ilium was 23 cm. The wrists measured 6½ in., ankles 8½. The eye examination* showed the following: O.D. media clear. Discs of a dirty yellow and a slightly indistinct border. The vessels were small. Through-

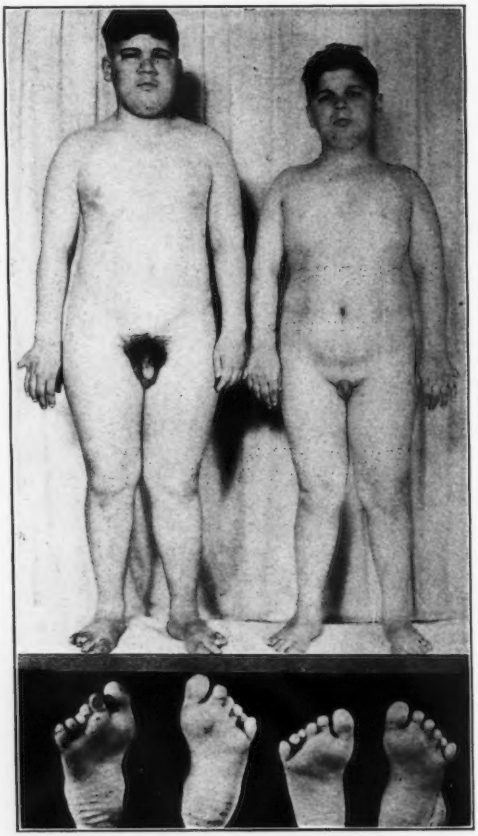

Figure 1. John (age 16) on left and Dominic (age 11), with the genital dystrophy, on the right.

out the entire fundus there was present considerable choroidal pigment absorption. In the macula and also in the portion of the near periphery there were a number of small, whitish, slightly elevated spots containing a small amount of pigment. Around the periphery, particularly the lower, there were a great number of retinal pigment deposits typical of pigment degeneration. Some of these were quite large. The diagnosis was pigmentary degeneration of the retina. O.S. findings were similar to O.D.

*Made by Dr. Alfred Cowan of the University of Pennsylvania.

Visual fields attempted but cooperation was poor. X-ray examination of the skull showed the sella turcica to be within normal limits. The differential blood cell count was within normal limits (Hb. 12.715, R.B.C. 4,550,000. W.B.C. 7100, Polys. 56 per cent, Lymph. 43 per cent, Eos. 1 per cent). The urinalysis showed nothing abnormal. The blood urea was 14.0 mg. per cent. The glucose tolerance test gave the following: Fasting, 85.0 mg.; 45 min. after ingestion of 100 gms. of glucose, 100 mg.; 2 hours after ingestion of glucose, 89.0 mg. The basal metabolic rate was slightly higher than normal (plus 17). The blood Wasserman reaction was negative. In school and community adjustment he was unable to follow simple directions. He was demanding, cried easily, was boisterous and did not get along well with the other children. He was destructive with the school furniture and

Figure 2. X-ray photograph of right hand. (John, age 16.)

equipment. He kept the class generally upset and was a bad influence. He started school at the age of six and repeated the first three grades. A psychological examination made in December, 1932, gave a diagnosis of high grade imbecile (I.Q., 40), which finding was subsequently confirmed in August, 1934, and in April, 1935. In December, 1934, he was committed to the N. J. State Colony for Feebleminded Males in New Lisbon. In the Institution it is noticed that he sleeps a great deal during the day and night. With the onset of darkness it is necessary for another boy to lead him about because of his night-blindness. (His parents told the senior author that the boy frequently would feel the walls to find the door.) In the Institution he has had frequent fights with other boys. He usually sits about, throwing stones and annoying everyone about him.

Case 2. Dominic, born December 29, 1923, was delivered normally, walked at one year, and had early dentition and bladder and bowel control. He talked at 2½ years. The physical examination as of 4-16-35 is as follows. He was 53¾ in. tall (min. for age, 53.3) and weighed 102 lbs. (max. for age, 79.4). Vision was difficult to ascertain because of the low mental level. The pupils reacted normally, and were equal and regular. There was no retinitis pigmentosa but there was a marked tessalated appearance. The optic discs were very pale. There was a high degree of myopia. The teeth were in good repair. The tonsils had been removed. The genitalia were very small, and the testes were undescended. Pubic hair was scanty. He had six fingers on each hand and six toes on each foot. The body build was distinctly feminine—large breasts, pendulant abdomen, knock-knees. The blood pressure was 117/70. The circumference of the head was 20¾ in. (average for age, 21.1), of the chest 31 in. (average for age, 26.1), of the abdomen 31½ in. (average for age, 23.3). The thighs at level of trochanter were 33¼ in. The span was 53 (min. for age, 63). The lower measurement was 25½ (min. for age, 26.3) and the upper measurement 28½ (max. for age, 28.7). Width at the ilium was 21 cm. The wrists were 6⅛ in., and the ankles 7¾ in. X-ray examination of the skull showed the sella turcica to be within normal limits. The hemoglobin was 12.9,

Figure 3. X-ray photograph of toes. (Dominic, age 11.)

the differential blood cell count was R.B.C. 5,200,000, W.B.C. 7000, Polys. 40 per cent, Lymph. 59 per cent, Eosin. 1 per cent. The urinalysis was within normal limits. The blood urea was 12.8 mg. per cent. The glucose tolerance test gave the following: Fasting, 76.0 mg.; 45 min. after 100 gms. glucose, 113 mg.; 2 hours after glucose ingestion, 91.0 mg. The basal metabolic rate was minus 7. The blood Wasserman reaction was negative. He started to school at 5 years of age and repeated the pre-primary grade three times and is now in the first grade. He shows no special abilities and accomplishes nothing. He likes to play and is friendly and is not a behavior problem. A psychological examination in December, 1932, gave a finding of low grade moron—I.Q. 50. This finding was confirmed in April, 1935.

Case 3. Leonard, born November 30, 1925, was delivered normally, walked at one year, acquired early bladder and bowel control, and talked at 2½ years. This boy died in August, 1933, of heart disease (congenital). He had seven fingers on each hand and six toes on each foot. He also had a Fröhlich's Syndrome but without retinitis pigmentosa. He had a strabismus with a visual defect of 20/40 20/70. He was not a discipline problem but was retarded in school. He played with children but was shy with

adults. He accomplished nothing in school. A psychological examination in December, 1932, gave a finding of low grade moron, I.Q. 52.

The lesion, a developmental defect, has been placed by Ornsteen (2) in the ectopic zone of the prosencephalon. Biedl (3) states that it is a "heredogenerative disorder consisting of a disturbance in the region of the mesencephalon, and of a chorioretinal disorder combined with other developmental abnormalities. It has nothing to do with a primary disturbance of the hypophysis. Whether the simultaneous occurrence of disturbances in the mesencephalon, in the retinal region and perhaps in other regions of the cerebrum, is the result of the common deviation of these regions from the primary anterior cerebral vesicle can so far only be assumed." Ornsteen (2), in his paper, gives some very convincing arguments for the location of the lesion so that we are in favor of his hypothesis.

Clay (4) recently made a review of the literature and his article contains some excellent pictures of fundi with retinitis pigmentosa. Cockayne, et al. (5), made the most recent review of the literature and reported that almost all of the cases had obesity, mental deficiency and retinal degeneration. Polydactylism and hypogenitalism were not always present. Reilly and Lisser (1) in their review found that only 25 of 77 cases had all the six cardinal symptoms. We agree with them that partial clinical combinations or subtypes require recognition and that unless all six cardinal symptoms are present a familial occurrence should be present. Several foreign authors (6), (7), believe that syphilis plays a part in the picture, but this is not borne out in our cases or in many others reported. Weil and Payeur (6) found a higher titer of hormone, about three to four times greater than normal, from the anterior pituitary in the urine of their case. Reilly and Lisser (1) found that there was nothing characteristic about the bone development as is true in our cases. They treated their patients with thyroid, pituitary and ovarian extract with good results. They reported an increased animation, improvement in vision and weight loss. Bing (8) treated his cases with calcium, thyroid and pituitary extract and produced a loss of weight, rise in basal metabolism and a greater animation and interest in surroundings. No improvement in vision was obtained. Menninger (9) treated one case with thyroid and pituitary extract and increased the I.Q. from 77 to 91. Our cases were not treated.

SUMMARY

Three brothers are described, each being affected to a different degree with a hereditary cerebral defect. All three had polydactylism, mental deficiency, pituitary dysfunction and some visual defect. The oldest brother (age 16) has also retinitis pigmentosa, while the next oldest (age 11) has a severe degree of myopia with a tessalated appearance of the retina. The youngest brother (age 8 at death two years ago) had a mild visual defect with strabismus. It is concluded that all cases, occurring in the same family, which have all or almost all the cardinal symptoms of the Laurence-Moon-Biedl syndrome should be so categorized. Isolated cases, without

other sibs being affected, and not having all the cardinal symptoms should not be included in the syndrome.

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FURTHER OBSERVATIONS ON THE TREATMENT OF HYPERINSULINISM WITH INSULIN*

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In 1933 I published my first report on the treatment of hyperinsulinism with insulin (1). The case was that of a young woman, 24 years of age, who was first seen in November, 1930. She complained of fainting attacks which often would last an hour. These attacks were growing in severity, but could be relieved by carbohydrate ingestion, if taken in time. The physical examination gave normal findings, but the glucose tolerance test showed a diabetic type of curve. She was advised to take food between meals.

She returned in February, 1933, at which time her symptoms were more marked, the fainting spells more frequent and more severe. Her weight had dropped from 124 to 108 pounds. The blood sugar at this time was 74 at noon and 56 in the evening. The glucose tolerance test was repeated the next day and gave a normal curve starting with 58 and ending with 65 at the end of the fourth hour.

She was placed on a high fat diet, 100 gm. of carbohydrate, 80 gm. of protein, 253 gm. of fat, a total of 3000 calories. She was also given 10 units of insulin, three times a day immediately after meals. Improvement in her condition was at once noted. She was kept on this routine for three months, during which time she gained about 22 pounds in weight. She felt normal in every way and was able to do more work than ever before. Her blood sugar level remained low. On June 14th insulin was withheld and the blood sugar fell as low as 28 mg. All insulin was then discontinued and she went on a normal diet. On this routine her symptoms did not return and the blood sugar has remained at a normal level. Recently she gave birth to a second child.

The second case was that of a business man, 41 years of age, who was first seen in June, 1934. In 1932 he had been diagnosed elsewhere as suffering from diabetes and had been treated by diet alone. The glucose tolerance curve at that time was definitely diabetic and the two subsequent blood sugar values were high. Physical examination gave normal findings except that the patient was overweight. In June and September, 1934, the blood sugar level was normal and the diabetes was thought to be well controlled. On October 16 the blood sugar values before each meal were 62, 66, 33 and the patient presented symptoms of hyperinsulinism. He was placed on a high fat diet but became more and more excited about his condition, showing symptoms of nervousness, hunger, sweating and exhaustion. On December 4 the glucose tolerance test was repeated and the curve indi-

*Read at the Nineteenth Annual Meeting of the Association for the Study of Internal Secretions, Atlantic City, N. J., June 10, 1935.

cated an increased tolerance, the values for the 3rd and 4th hours being 33 and 34. He remained on the high fat diet a month longer and on January 11 insulin was started, 20 units one-half hour after each meal. Improvement was noted immediately after institution of the insulin treatment. The blood sugar level did not change appreciably but there were no hypoglycemic reactions at any time. After two and one-half months of this routine, during which time he worked hard, insulin was discontinued

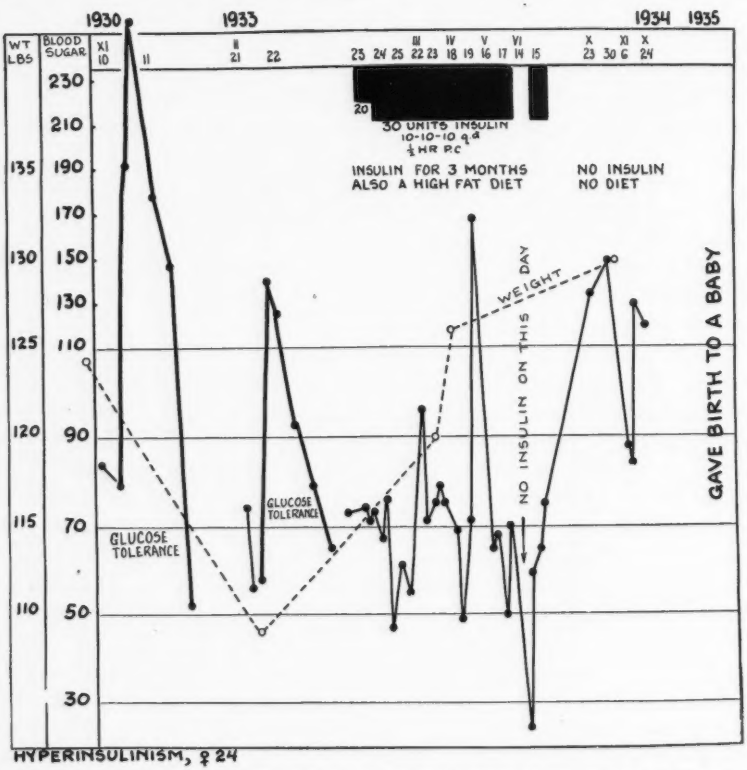

Chart 1. A case of hyperinsulinism in a woman 24 years of age, treated with high fat diet and insulin.

and he went on a normal diet. Two subsequent checks did not indicate any marked change of the blood sugar level, but the patient remained entirely free of any symptoms.

The third case was that of a physician, 71 years of age, who was first seen in August, 1934. He complained of hunger spells, weak spells and fainting. He had had to eat candy at night to relieve these symptoms. A blood sugar examination made elsewhere in November, 1933, gave a value of 50. The above symptoms were of four years' duration and were growing in intensity. Five blood sugar values determined at one-hour intervals

were 55, 65, 72, 60, 77. He was on a high fat diet and two and one-half weeks later the blood sugar values were again determined, starting at noon and continuing hourly until midnight with the following figures: 82, 87, 96, 83, 98, 83, 83, 99, 92, 76, 85. These figures are normal but the symptoms of hyperinsulinism were still present and he was obliged to take food twice during the night to relieve his hunger spells. The following day insulin was started in dosage of 20 units one-half hour after each meal. The blood sugar value stayed at the same level but the symptoms disappeared. On the sixth day, while at the hospital, the patient had a coronary occlusion, following which all insulin was discontinued. A month later the blood sugar value was 65 at noon and 41 in the evening. Insulin was resumed in a step-like manner so that on the seventh day he was again receiving 20 units after each meal. Improvement was again noted. He was introspective and convinced in his own mind that he had a pancreatic tumor and at his request an operation was performed on December 1. No abnormality of the pancreas was found. Following the operation he received no insulin and his blood sugar level was higher and within normal range and he was symptom free. Two and one-half months later his blood sugar values were 50, 48, 52 and insulin was resumed. A month later, while the patient was still on insulin, the blood sugar values were taken throughout the day and ran as follows: 90, 136, 166, 163, 122, 109. On May 1, 1935, insulin was discontinued and two weeks later the blood sugar values were 46, 52, 58. He feels fine and at present is taking Lextron, takes nothing to eat between meals and is much stronger and energetic.

These three cases show the progress of such cases of hyperinsulinism on insulin. It must be kept in mind that hyperinsulinism is not a simple problem which can be solved by one single procedure. Perhaps only the cases of functional hyperinsulinism will react. By this is meant that in the functional type there is a deranged mechanism of insulin production or regulation. In the anatomic type there is an adenoma of the islands. The latter are beyond any nervous regulation and produce insulin uncontrolledly. It is probably only the functional type that we can help to regulate by the exogenous use of insulin given after meals before the blood sugar has a chance to stimulate the secretion of insulin by the pancreas. If hyperglycemia can be avoided in this manner, it should be possible to avoid the increased stimulus and thus to eliminate the unpleasant and trying symptoms from which these patients suffer and possibly in time also to control the accompanying hypoglycemia. It is known that the pancreas of a diabetic can be trained to secrete more insulin by teasing it with excess of carbohydrate under proper conditions and it was thought to be possible to train the pancreas to secrete less insulin by placing it, so to speak, at physiologic rest by the supply of exogenous insulin.

In the first case perfect results were obtained and the symptoms were entirely eliminated immediately after the institution of a high fat diet and 10 units of insulin three times a day. The patient began to gain weight and was normal in every way. This improvement persisted after insulin

was discontinued and some months later the blood sugar level became normal. This, I think, is final proof that a complete psysiological readjustment was obtained as was also the fact that the patient was able to go through a pregnancy in a normal way without complications.

The second case presents a very interesting problem. In 1932 the patient was diabetic and in 1934 showed hyperinsulinism. A similar picture was seen previously in a physician 61 years of age who was a severe diabetic when first seen and who died in hypoglycemic shock (2) in the course of one and a half years. At postmortem a marked hypertrophy of

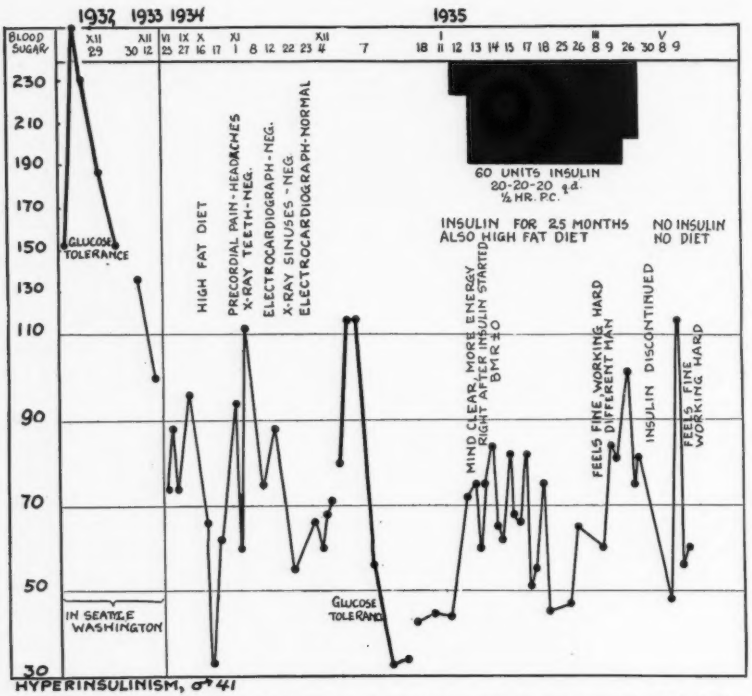

Chart 2. A case of hyperinsulinism in a man 41 years of age, treated with high fat diet and insulin.

the Islands of Langerhans was found. Naturally the question arose whether in this second case a similar picture was being presented. If so, he would not respond to insulin and if he did respond this should be proof that we were dealing with a functional case of hyperinsulinism. He responded well to insulin and it has been over two months since the insulin was discontinued without any suggestion of return of symptoms. The blood sugar level is still low and it may be that a return of blood sugar to normal boundaries will occur later as in the former case.*

*That this has actually happened is indicated in two later examinations.

In the third case the picture is more uneven. The symptomatology is the same and definite. At the beginning the blood sugar level rose after the high fat diet but the symptoms remained. When insulin was started, the symptoms began to improve, but unlike in the other two cases they did not cease entirely from the beginning of treatment. The coronary thrombosis was also a disturbing factor in this case, although I do not believe that insulin had anything to do with it. It will be noted on the chart that the blood sugar value at that time was normal. There was no marked lowering of the blood sugar value when insulin was given one-half hour after meals, during the postprandial physiological rise of blood sugar, but rather an evening of the curve. The patient improved, insulin was discontinued because of the cardiac upset but in a month it had to be resumed as

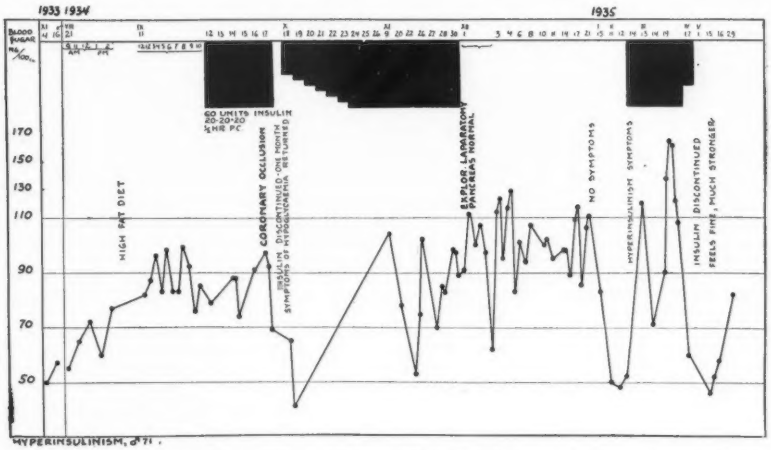

Chart 3. A case of hyperinsulinism in a man 71 years of age, treated with high fat diet and insulin.

the symptoms returned. Following this there was a considerable improvement. The exploratory laparatomy was made at his own request but no abnormality was found. He went to Florida in February and while there symptoms of hyperinsulinism returned. Insulin treatment was again started and continued for two months with improvement. At present he feels fine, is strong and well with the exception of a precordial pain on exertion. His blood sugar value is low.†

It seems in this case that there was improvement following each course of insulin which continued over a period of time, but I believe that the insulin treatment should have been continued over a longer period without interruption (about three months at a time) in order to get the most out of it. Shorter periods do not seem to bring about readjustment.

†On later examination the blood sugar level had risen to normal.

SUMMARY

Three case histories of hyperinsulinism are reported. The findings indicate that the condition is either functional or anatomic. In the functional type the patient responds to treatment with high fat diet and insulin in 20 unit dosage one-half hour after each meal. It is necessary to continue the treatment over a period of three months. It is quite possible that we may be able to differentiate the two types in this manner as the functional type should respond to insulin whereas the anatomic type should not. Two of the patients herein presented seem to be entirely cured of hyperinsulinism by this method of treatment. The first case especially was severe and of long duration. The procedure is simple and the time required in the hospital is but a few days, just long enough to make sure that the patient will react and to teach him how to administer the insulin.

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SYNDROME ACCOMPANYING DEFICIENCY OR ABSENCE OF THE OVARIAN FOLLICULAR HORMONE*

STUDY OF 197 CASES

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In an article published in 1931, the author (1) described the symptoms presented by 136 castrated and menopausal women. This work includes additional cases, plus a new group of 48 women having involutional melancholia, totaling 197 patients.

Ovarian hypofunction may be due to pathological conditions such as cystic degeneration or inflammatory processes in or adjacent to the ovaries —salpingitis, appendicitis, etc.—which may cause degeneration in the glands. It may be secondary to constitutional disease processes, as some anemias, tuberculosis, malignancies other than pelvic, etc. Vitamin deficiency in the diet may cause it. It may be primary as in some cases of eunuchoidism with late development of the secondary sexual characteristics in which the ovaries may never attain full development and function. It may be secondary to anterior pituitary deficiency as in some types of infantalism, so-called bilobar-pituitary insufficiency, preadult or postadult. It may occur after partial castration where one ovary has been removed or only a small part of one ovary remains. It will be complete where both ovaries are removed unless there be accessory ovarian tissue. It always occurs at the climacteric.

The syndrome which accompanies ovarian hypofunction may be divided into objective signs and subjective symptoms. Among the objective signs are various types of menstrual disorder, such as irregularity, hypomenorrhea, decreased duration and finally amenorrhea. Menorrhagia and metrorrhagia also occur at times but are more frequent in women who are approaching the natural menopause.

Obesity of the gonadal type, characterized by deposition of fat over the trochanters, mons veneris and in the breasts, occurs in many of these women after they reach the age of approximately 30 years. However, gonadal obesity may be combined with the pituitary and thyroid types. Atrophy of the genitals, the glandular structure of the breasts and loss of genital and axillary hair may occur.

The subjective symptoms accompanying ovarian hypofunction or afunction render the patient more uncomfortable than do the objective signs. They may be classified as (1) nervous, (2) circulatory and (3) general. A proper evaluation of their significance is necessary, as these symp-

*Read before the Nineteenth Annual Meeting of the Association for the Study of Internal Secretions, June 11, 1935.

toms are frequently the chief basis of diagnosis. These symptoms have been listed and classified in the accompanying tables.

A STUDY OF 197 CASES

That these symptoms do accompany ovarian hypofunction is conclusively shown by reference to Tables 1, 2 and 3, which are tabulated from histories of 53 castrates observed by the author.

TABLE 1
FREQUENCY OF NERVOUS SYMPTOMS

	53 Castrates Per Cent	96 Menopause Per Cent	48 Involutional Melancholia Per Cent
Nervousness, subjective	100 0	92.7	100.0
Excitability	84.2	72.9	100.0
Irritability	68.0	61.4	95.8
Headache	36.0	50.0	83.3
Occipitocervical pain	58.0	37.5	56.2
Decreased memory and concentration	51.0	54.1	95.8
Depression, crying	71.7	60.4	100.0
Psychosis	20.8	35.4	100.0
Formication	23.1	23.9	29.2
Sleep disturbed	66.0	59.3	72.9

TABLE 2
FREQUENCY OF CIRCULATORY SYMPTOMS

	53 Castrates Per Cent	96 Menopause Per Cent	48 Involutional Melancholia Per Cent
Hot flushes	94.3	91.6	81.2
Tachycardia, palpitation, dyspnea	54.7	72.9	79.0
Vertigo	68.0	71.8	62.5
Scotomata	43.4	50.0	12.5
Cold hands and feet	43.4	23.9	81.0
Numbness, tingling	37.7	29.1	77.1
Pulse average per minute	76.	78.3	76.
Blood pressure, average	123/76.	138/88.6	128/76.
Pulse pressure, average	47.	50.	52.

TABLE 3
FREQUENCY OF GENERAL SYMPTOMS AND SIGNS

	53 Castrates Per Cent	96 Menopause Per Cent	48 Involutional Melancholia Per Cent
Lassitude, fatigability	75.0	78.1	98.0
Constipation	72.5	72.9	83.3
Vague pains	Not recorded	Not recorded	77.1
Obesity	28.0	51.1	8.33
	Chiefly gonad (43 cases recorded)	Pit. and thy. (86 cases recorded*)	Moderate obesity (4 cases recorded)
Menstrual disorder	100.0	97.7	100.0
Amenorrhea	94.3	41.5	37 more than 6 mos. 11 less than 6 mos.
Basal metabolism	+6.4 (6 cases)	+8.2 (17 cases) −7.0 (3 cases)	See special reference

*Obese before menopause, 18; after menopause, 26.

That this same train of symptoms is found with striking parallelism in the menopause and in involutional melancholia is also shown by Tables 1, 2 and 3, in which are tabulated the symptoms complained of in 96 cases of natural menopause and 48 cases of involutional melancholia.

TABLE 4

SYNDROME ACCOMPANYING DEFICIENCY OR ABSENCE OF THE OVARIAN FOLLICULAR HORMONE IN 197 CASES (53 CASTRATES, 96 MENOPAUSE, 48 INVOLUTIONAL MELANCHOLIA)

Order of Frequency of Symptoms	Per Cent
1. Menstrual disturbances	99.2
2. Nervousness, subjective	97.6
3. Hot flushes	89.0
4. Excitability	85.7
5. Fatigability and lassitude	83.7
6. Depression and crying	77.4
7. Constipation	76.2
8. Irritability	75.1
9. Tachycardia, palpitation and dyspnea	68.8
10. Vertigo	67.4
11. Decreased memory and concentration	66.8
12. Sleep disturbed	66.1
13. Amenorrhea	57.6
14. Headaches	56.4
15. Psychosis	52.2
16. Occipitocervical aching	50.6
17. Scotomata	49.4
18. Numbness and tingling	48.3
19. Cold hands and feet	35.3
20. Formication	25.4
21. Vague pains (recorded for involutional melancholia)	77.1

In Table 4 the symptoms accompanying ovarian hypofunction are combined in the order of their frequency as found in 197 cases, consisting of 53 castrates, 96 natural menopause and 48 involutional melancholia.

Under "Onset of Symptoms," Table 5, it will be noted that in nine patients the symptoms were delayed. The average duration was two years, one month. In four cases the delay was two and a half years, three years, five years and six years, respectively. It is possible that these women did not have complete bilateral ovariectomy or that they might have had some supernumerary ovarian tissue. A fragment of ovarian tissue is not sufficient to carry on normal function and probably scar tisue formation and contraction following the operation may cause it to atrophy. In 12 women who had attempts at menstruation following operation the flow was scant and irregular. Fifty of the 53 castrates had complete amenorrhea before consulting me.

Werner (3) and associates are of the opinion that involutional melancholia is only an exaggeration of the menopausal syndrome and that it is due to the same cause.

TABLE 5

MISCELLANEOUS DATA—53 CASTRATES

Present average age	33.3 years
Average age of castration	27.2 years
Onset of symptoms:	
Immediate (44)	83.0%
Delayed (9)	17.0%
Period of delay	6 mos., 2; 1 yr., 2; 1.5 yr., 1; 2.5 yr., 1; 3 yrs., 1; 5 yrs., 1; 6 yrs., 1
Average duration of delay in 9 patients	2.1 years
Flow after castration, scant and irregular (12)	23%
Amenorrhea at present (50)	94.3%
21 castrates had had 31 children.	
Cause for castration	Salpingitis (abortion—gonorrhea)

TABLE 6

MISCELLANEOUS DATA—96 MENOPAUSE

Present average age	44.1 years
Average age at onset of symptoms	40.8 years
Nature of menstrual disturbance:	
1. Irregularity (62 cases)	64.6%
2. Scantiness (50 cases)	52.0%
3. Menorrhagia (19 cases)	19.8%
4. Dysmenorrhea (17 cases)	17.7%
5. Metrorrhagia (6 cases)	6.3%
6. Amenorrhea (40 cases)	41.5%
Average length of amenorrhea (40 cases)	26.2 months

Table 7 gives some of the data on 48 cases of involutional melancholia. Of these 48 subjects only four had moderate obesity; these cases usually show a loss of weight which increases to normal or perhaps above with recovery.

Of 73 women at the menopause, six had not had children and 67 women had borne 298 children, an average of 4.44 each. Twenty-one castrates had had 31 children. Twenty-two women of record admitted having had 38 abortions, mostly induced.

DISCUSSION

The term menopause, literally meaning cessation of menstrual flow, is commonly used to designate that critical period in a woman's life more correctly spoken of as the climacteric. Menstrual pause may occur at any time during the menaeme from various causes. The menopause is more than a pause or cessation of menstrual flow. This is only one of the phenomena which occur at this time. It is the one sign which is objective and therefore attracts most attention.

The pathogenetic mechanism of menopausal symptomatology is not limited to insufficiency of the ovaries but is the result of a complex endocrine crisis which varies in different individuals. In this crisis the predominating feature is gonadal insufficiency but other glandular disturbances occur subsequently and form an essential part of the complex. Because of the major importance of the gonads in the endocrine system during

TABLE 7

MISCELLANEOUS DATA—48 INVOLUTIONAL MELANCHOLIA

Present average age	49.4 years
Average age of onset of symptoms	47 years
Amenorrhea for more than 6 months	37 patients
Menstruation of disordered type during last 6 months	11 patients

BASAL METABOLIC RATE, 36 CASES

Minus 1 to minus 10%	10 cases	0 to plus 10%	10 cases
Minus 11 to minus 15%	5 cases	Plus 11 to 15%	2 cases
Minus 16 to minus 20%	1 case	Plus 16 to 20%	2 cases
Minus 21%	1 case	Plus 21 to 30%	3 cases
		Plus 35 to 64%	1 each

active sexual life, insufficiency or cessation of function frequently causes imbalance in other interrelated glands such as the anterior pituitary, at times the posterior pituitary, the thyroid, the adrenals (medulla and in some instances the cortex).

With this disturbance of function in the ovaries and other interrelated glands we have a secondary disturbance of the delicate equilibrium existing between the two divisions of the autonomic nervous system with the production of the subjective symptoms described. In other words, most of these symptoms are the result of autonomic nervous system instability secondary to glandular imbalance.

The onset of symptoms and their degree of severity may depend upon the rate of cessation of ovarian function. If the cessation is a gradual process, the interrelated glands, such as the pituitary, the thyroid and the adrenals, may respond to the needs of the body or readjust their function accordingly; if it be more sudden, as in castration, the disturbance of equilibrium of the organs of internal secretion and the autonomic nervous system will be more severe.

There are three periods in a woman's life when she is apt to have trouble with her thyroid gland: (1) at puberty, (2) during any pregnancy, (3) at the menopause. If a woman is potentially hyperthyroid, i.e., if she has a goiter that has given evidence of causing trouble before, or if she has a colloid goiter with hidden adenomata within, or a frankly adenomatous goiter, she is in great danger at any of these periods of developing hyperthyroidism. I have had women who developed frank hyperthyroidism at these critical periods, but they probably had abnormal thyroids which only needed some unstabilizing influence to initiate their hyperactivity.

It has been my experience that the vast majority of these women have an approximately normal basal metabolic rate. Reference to Table 3 shows that the metabolism of six castrates averaged plus 6.4 per cent. In 20 patients at the natural menopause in whom basal tests were recorded 17 averaged plus 8½ per cent and three averaged minus 7 per cent. Table 7 gives the basal metabolic rate of 36 women having involutional melancholia. The rate in these 36 subjects (in the others the rate could not be obtained) ranged from minus 21 per cent to plus 64 per cent. However, these higher rates were obviously inaccurate for we do not believe that any patient was hyperthyroid. The two patients having metabolic rates of plus 35 and plus 64 per cent made complete recoveries on theelin.

CONCLUSIONS

This group of symptoms is primarily initiated by ovarian hypofunction. The ovarian hypofunction may result from the various causes enumerated. Secondary to the ovarian hypofunction there may be disturbance of function of the pituitary, the thyroid and the adrenals, with consequent imbalance of the delicate equilibrium normally existing between the two divisions of the autonomic nervous system.

These symptoms occur in castrates and in many women at the menopause, during which conditions biological tests show an excessive amount of follicle-stimulating hormone of the anterior pituitary in the blood. In the first instance there are no ovaries to respond to stimulation and in the second the ovaries do not respond.

Involutional melancholia is an exaggeration of the menopausal syndrome.

It is easy enough to diagnose ovarian disturbance when it is associated with menstrual disorder or when it occurs at about 40 years of age or in castrates, but when the symptoms occur before time for the menopause and without much menstrual disorder, we may fail to recognize ovarian hypofunction as a possible cause. Finding no organic lesion or evidence of disease in these patients they may be diagnosed as neurasthenics and are buffeted about from one physician to another without relief.

It is the experience of the author that these three groups of patients derive the greatest benefit from the administration of estrogenic hormones. The treatment of the various menstrual disorders, in which several well-known endocrine factors are involved, is much more unsatisfactory.

SUMMARY

This article is based upon an analysis of the objective signs and subjective symptoms presented by 197 women having deficiency or absence of the ovarian follicular hormone. This group of patients consists of 53 castrates, 96 women in the menopause and 48 subjects having involutional melancholia. The subjective symptoms are classified as nervous, circulatory and general.

That these symptoms do accompany ovarian hypofunction or afunction is evidenced by their regularity of occurrence in 53 castrates studied. This same train of symptoms is found with striking parallelism in the menopause and involutional melancholia.

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THE SIZE AND STRUCTURE OF THE THYROID GLAND OF THE CAT AFTER THE ADMINISTRATION OF IRRADIATED ERGOSTEROL

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Seasonal changes in the structure of the thyroid gland, a hyperplasia occurring during the winter months, have been described by Seidell and Fenger (1912) and by Herzfeld and Klinger (1922). These changes were believed to result from seasonal differences in temperature (Cramer, 1916; Mills, 1918). That differences in sunlight might be equally important seems not to have been considered. Bergfeld (1930) found a definite relationship between the function of the thyroid of the rat and light, darkness interfering with proper functioning. Rosenkranz (1931) found that rabbits kept in a dark room or oxen confined to stalls show considerable increase in the parenchyma, with a decrease in the number of follicles and colloid content. Animals kept on the same diet and exposed to sunlight did not show these changes. Similar hyperplasias have been observed in rickets by Murray (1923), Sorour (1923) and Stoltenberg (1929). Since the thyroid gland is found in the colloid or "resting" state during the summer months, months with a high ultraviolet content in the sunlight, it suggests that these changes may result from the greater amount of irradiated ergosterol (direct irradiation of the skin and irradiated foods) available at this season. In the present investigation, the effect of various levels of intake of irradiated ergosterol (viosterol) on the size and structure of the thyroid gland was studied.

METHODS

Young cats were confined to small laboratory cages. These were kept in a room with a northern exposure, the light coming through two large windows. The temperature was kept fairly constant at about 25° C. (range 22° to 29° C.). All experiments here reported were carried out during the months from October 14 to March 21. Irradiated ergosterol* was diluted to the desired potency with corn oil and administered per os. The following dilutions, 25D, 50D, 100D, 150D, 200D, 250D and 1000D, were used, each cat receiving one cubic centimeter of oil per day. The oils were administered over a period of 21 days, after which time the cats were killed, the thyroids removed, weighed and microscopic sections prepared.

RESULTS

There were no significant changes in the structure of the thyroid glands of cats receiving irradiated ergosterol until after the administration daily

*The irradiated ergosterol used in these experiments was furnished us through the courtesy of the Mead Johnson & Co.

of one cubic centimeter of oil containing a potency of 250D or more. At this level of intake, there was a definite change in the microscopic structure of the thyroid gland. Whereas in cats receiving oil containing no

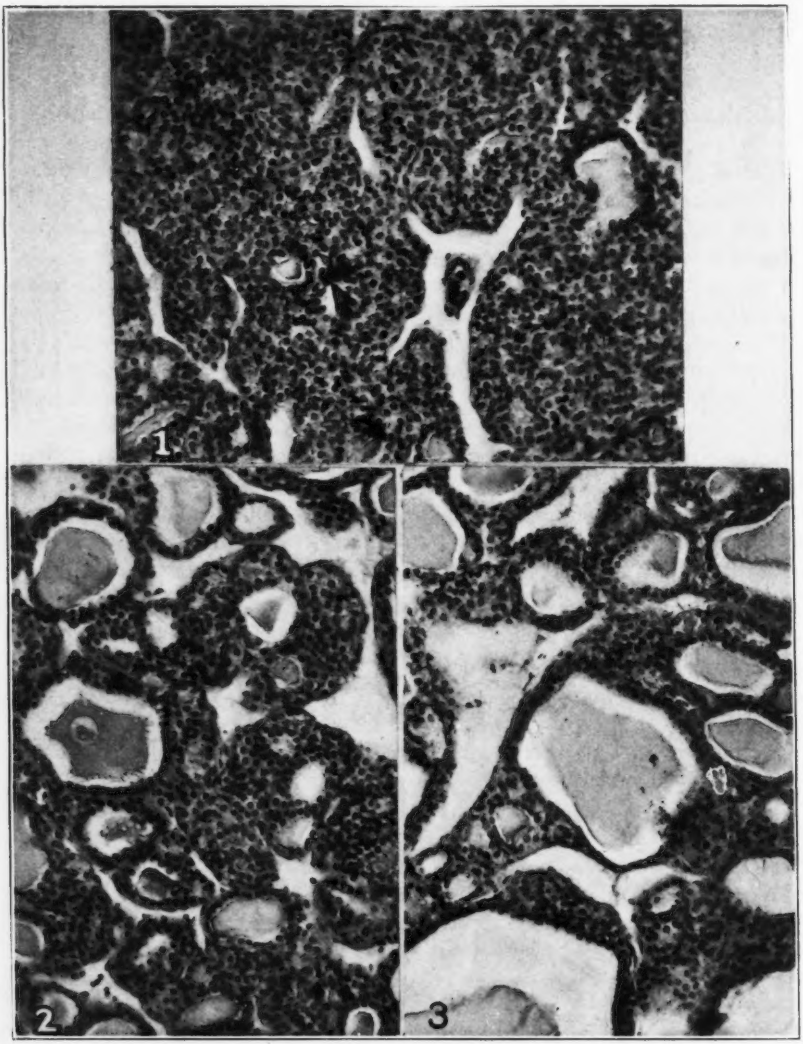

Figure 1. Control. Corn Oil 1 cc. per day. Magnified 200 X.
Figure 2. Irradiated Ergosterol 250 D in Corn Oil. 1 cc. per day. Magnified 200 X.
Figure 3. Irradiated Ergosterol 1000 D in Corn Oil. 1 cc. per day. Magnified 200 X.

ergosterol the vesicles were small with many vesicles completely collapsed (Fig. 1), those receiving irradiated ergosterol 250D or more showed a predominance of moderate and large vesicles and abundant colloid (Figs.

2 and 3). The height of the lining epithelium varied with the size of the vesicles, being columnar in the very small or collapsed vesicles and flattening out to cuboidal in the larger ones. A summary of all experiments is given in Table I.

Marine and Lenhart (1911) called attention to the extremely sensitive nature of the thyroid, which fact has been amply confirmed by many studies since that date. This advises caution in attributing the observed changes in structure to any one factor. Following the administration of large amounts of irradiated ergosterol there is a hypercalcemia, loss of appetite and depression. These symptoms were always manifest in those animals showing the most marked changes in the microscopic structure of the thyroid. Watson (1907), Missiroli (1910), Douglas (1915) and Jackson (1916) have shown that inanition may cause changes in the structure of the thyroid similar to those found above. It is possible that the inanition resulting from the administration of toxic amounts of irradiated ergosterol may have caused the changes in structure observed here. Mills

TABLE I

THE MICROSCOPIC STRUCTURE OF THE THYROID GLAND OF YOUNG CATS FOLLOWING THE ADMINISTRATION OF IRRADIATED ERGOSTEROL

Number of Experiments	Treatment	Microscopic Appearance
6	None	Vesicles small or collapsed. Cells generally columnar. Moderate amount of colloid.
5	Corn oil	Same as controls.
10	Irrad. Erg. up to 250 D	Same as controls.
2	Irrad. Erg. 250 D	Vesicles moderately enlarged. Considerably more colloid than in controls.
5	Irrad. Erg. 1000 D	Vesicles large and well filled with colloid.

(1918) found morphine decreased the activity of the thyroid. Hypercalcemia and the resultant depression may exert a similar action. More study is required before a direct correlation between these changes and irradiated ergosterol can be established. Non-toxic amounts cause no changes in the microscopic structure of the thyroid gland of young cats.

Marine and Lenhart (1909) found that the stainable colloid of the thyroid varies directly with its iodine content. Seidell and Fenger (1912) observed that there was, in general, an inverse relation between the size of the gland and its iodine content. With these observations in mind, an attempt was made to determine whether there was any correlation between the weight of the gland and its content of colloid under the conditions of these experiments. The normal weight of the thyroid of the cat was found to be quite variable, there being only a low correlation between body weight and gland weight. No correlation was found between the weight of the gland and its content of colloid or the experimental procedure in these experiments.

SUMMARY

1. The administration of non-toxic amounts of irradiated ergosterol in corn oil to young cats caused no significant alterations in the normal structure of the thyroid gland.

2. The administration of toxic amounts of irradiated ergosterol resulted in marked alterations in the microscopic structure of the thyroid. Whereas in the normal gland the vesicles were small or collapsed, after the administration of toxic amounts the vesicles were large and the colloid abundant. Some of the difficulties in attributing this change to a direct action of irradiated ergosterol are pointed out.

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MENOPAUSAL HYPERTENSION

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The menopause is an important endocrinal epoch in the life of the human female. There is a definite symptom-complex which accompanies it whether it is spontaneous or artificial. It is characterized by metabolic, vasomotor, and, not infrequently, vascular changes. The most significant vascular changes are those of gradually increasing hypertensive states which, if permitted to continue, will result in permanent hypertension and consequent arteriosclerotic alteration.

That there is an evident hormonal imbalance existing at this time is generally conceded. Hoskins and Wheelon (1) have shown experimentally that castration results in a marked irritability of the vasomotor apparatus. At the time this work was done they were of the opinion that a small amount of ovarian tissue or ovarian grafts would prevent the appearance of the artificial menopause, indicating that a hormone was involved which acted as a sympathetic depressor. This suggested the possibility of specific replacement therapy in the form of ovarian follicular hormone (theelin) with the hope of striking some semblance of normal incretory balance.

Thirteen subjects presenting a true menopausal symptom-complex with varying degrees of hypertension were selected for treatment. The histories of the first three patients are presented in detail. These were selected because they were under observation for a sufficient length of time previous to the onset of menopause to permit us to demonstrate that their hypertension developed at the onset of menopause.

CASE REPORTS

A spinster with spontaneous menopause, aged forty-two years, had been under observation for six years for multiple neurofibromata and subacute polyarthritis. The blood pressure during this time had never exceeded 130/80. In May, 1934, she began having hot and cold flashes. No alteration in her menses was noted until two months later, when there was a cessation; there has been no recurrence of the periods. During this time the systolic blood pressure range was from 160 to 190. Theelin therapy in a maximum dosage of 1000 international units per cc. (1 cc. of commercial theelin in oil) was administered twice weekly for a period of four weeks. The therapy produced relief from the flashes, and the blood pressure receded to 140/95.

A widow, aged forty years, with surgical menopause had been under observation for a period of seven years for duodenal ulcer. The blood pressure during this time never exceeded 130/80. A hysterectomy for uterine fibroids was performed with immediate onset of menopausal symptoms consisting of hot and cold flashes. Within six months her blood pressure rose to 200/105. Treatment with 2 cc. of the aqueous solution of commercial

MENOPAUSAL HYPERTENSION

Case Number	Age Years	Average Blood Pressure				Duration of Treatment	Blood Non-protein Nitrogen	Blood Sugar Mgm.	BMR Per Cent	Urine	EKG	Kahn
		Before Treatment		After Treatment								
		Systolic	Diastolic	Systolic	Diastolic							
1	42	160–190	90	140–160	95–115	5 months	26 mgm.	99	− 9	Negative		Negative
2	40	190–200	90–105	130–140	90	3 years	28 mgm.			Negative		Negative
3	41	190	100–120	130–140	80– 90	2 years	40 mgm.	90	− 5	Negative		Negative
4	48	230	140	164	100	2 years	37 mgm.		+11	Negative		Negative
5	48	250	140	150	110	3 months	31 mgm.		+ 5	Negative		Negative
6	57	175	100	135	90	1 year	28 mgm.	105	+.6	Negative	Slur QRS Cor. T.	Negative
7	47	200	120	145	100	2 years	42 mgm.	120	+ 6	Negative	Notch QRS	Negative
8	56	215	120	150	100	2 years	28 mgm.	105	+ 9	Negative		Negative
9	50	240	140	190	110	2 years	40 mg n.		+30	Negative	Negative	Negative
10	52	205	120	150	90	4 years	48 mgm.		+16	Negative	Negative	Negative
11	55	160	90	130	80	3 months	31 mgm.	105	+ 8	Negative	Notch QRS	Negative
12	43	195	120	150	90	2 years	Negative		− 6	Negative		Negative
13	46	180	110	155	115	3 years	34 mgm.		+ 2	Negative		Negative
Average...	48	209.7	115.1	149.1	84.2	1.8 years	34.4 mgm.	104	+ 5.2	Negative	Negative	Negative

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theelin, which has only one-third the potency of 1 cc. of theelin in oil, was administered three times weekly for two months before the pressure fell to 140/90. She has been under constant observation for two years. Withdrawal of treatment for a period longer than one month results in a rise of pressure to as high as 180/100.

A spinster, aged forty-one years, with roentgen menopause had been under observation for two years because of exceedingly severe dysmenorrhea associated with prostrating headaches. The menses were normally rhythmic. The blood pressure during this period never exceeded 140/85. Many forms of therapy were employed to give relief from her menstrual symptoms, but without avail. She was then subjected to Roentgen ray sterilization, resulting in a complete amenorrhea. Within a few weeks frank menopausal symptoms consisting of hot and cold flashes and profuse sweats occurred. The blood pressure rose to 190/100. Commercial theelin (2 cc. of the aqueous solution) was administered three times weekly for over a period of a month before the subjective menopausal symptoms were controlled and the blood pressure readings dropped to 140/90.

DISCUSSION

The above three cases are emphasized because they illustrate the clinical dictum that hypertension and menopause are frequently concomitant. The remaining ten subjects presented themselves during various phases of the menopause associated with its true symptom-complex and with the increase in vascular tension as indicated. The entire thirteen were all subjected to a routine diagnostic survey to exclude in so far as possible other etiological factors.

The age range was from forty to fifty-seven with an average of forty-eight years. The average systolic pressure before treatment was 200.7, and the average after treatment was 149.1. The average diastolic pressure before treatment was 115.1, and the average after treatment was 84.2. The average duration of the treatment period was 1.8 years. The blood chemistry was essentially normal except in Case 10, in which there was a slight increase of blood nonprotein nitrogen to 48 mg. Blood sugar values were entirely normal as were the basal metabolic rates. Urinalyses in no instance presented significant changes. There were only three who presented mild electrocardiographic alterations. The Kahn tests were negative throughout.

The blood pressure readings were all determined in a routine manner usually after the patient had had a rest period of at least ten minutes after arrival at the office. The majority of these, probably ninety per cent, were taken by an assistant to eliminate any personal bias. While it is true that there are possible variations in pressure readings obtained in individuals by different observers, at the same time a trained assistant or physician engaged in clinical work must have some personal standard by which he evaluates such readings.

In addition to the menopausal symptomatology presented by all patients, those in whom the pressure was markedly elevated suffered from the usual subjective hypertensive symptoms, the commonest of which is

headache varying from a dull to a prostrating or severe type. Only one patient, Case 10, presented subjective cardiac symptoms.

Treatment. No medication other than the ovarian follicular hormone (theelin) was administered in any of the described cases. We believe this to be a definite specific organotherapeutic substance and also believe that its only clinical indication is in those instances in which true ovarian failure can be diagnosed. The menopausal state giving rise to its symptom-complex with or without hypertensive changes we believe to be such an indication. It is granted that there are many causative factors concerned in the production of essential hypertension, but it is believed that the climacteric is an important one. Our factual evidence for this supposition is that clinically a major percentage of hypertensive vascular disease occurs during this period of life. Previous negative results have been published with this specific glandular medicament in the treatment of hypertensive disease, but in these publications no attempt was made to associate the hypertensive state with ovarian failure. No claim has been made that this substance has any general vaso-depressant action, and, therefore, it is not indicated unless ovarian failure is present.

The cardinal rule of replacement organotherapy is to administer an adequate amount of the specific glandular substance indicated. Routinely in all menopausal states it has been our method to give this product in dosage of 2 cc. of the aqueous solution three times weekly. If the subjective symptomatology with this dosage is not definitely improved at the end of two weeks, it is given daily in this dosage. If this, too, proves inadequate, our daily dosage is increased to 3, 4 or 5 cc. Since theelin in oil has been obtainable on the market the treatment has been much simplified in so far as frequency and bulk of dosage are concerned. This product has six times the potency of the aqueous solution and a slower rate of absorption.

Our best guide for dosage and frequency is the subjective evidence evinced by the patient herself. Specifically, the control of the vasomotor instability by theelin has served best the aim of therapy. Usually when this occurs, a primary drop in pressure occurs. Continuation of treatment, too, is more or less individual. In a large degree it, also, depends upon the subjective symptomatology. The patients are instructed to return for further injections at the first sign of a return of their various complaints. Intervals of freedom from symptoms from a few weeks to several months have been noted. With a return of the vasomotor instability there was usually again an abnormal rise of the blood pressure. The great difficulty in this form of treatment is that one cannot assure the patient of permanent results, and they must be instructed that therapy should be continued for an indefinite period until nature achieves a normal hormonal balance in the endocrine structures involved.

SUMMARY

In the series of 13 subjects of menopausal hypertension herein presented there has been a substantial reduction of the hypertension and

amelioration of all the associated symptoms after the administration of theelin therapy. The data secured indicate that hypertension frequently develops during the menopause and there is an evident incretory imbalance present at that time. It appears that there is an actual lack of a follicular hormone (theelin) and that its replacement is logically indicated.

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STUDIES ON CONDITIONS OF ACTIVITY IN ENDOCRINE ORGANS.* XXX. THE NERVOUS CONTROL OF THE ANTERIOR HYPOPHYSIS AS INDICATED BY MATURATION OF OVA AND OVULATION AFTER STIMULATION OF CERVICAL SYMPATHETICS

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The physiological relationship between the anterior hypophysis and the thyroids and ovary, respectively, is delicately balanced; and its equilibrium can be easily disturbed by permitting the hypophyseal thyreotropic and gonadotropic substances to fall below or exceed their normal concentration in the organism. Thus the rate of secretion of these essential principles is quickly reflected in the functional state of the thyroids and ovary, i.e., these organs atrophy rapidly after hypophysectomy, or show evidence of increased functional activity if the normal secretion of the animal's own pituitary is supplemented by injections of an active anterior hypophyseal extract (1, 2, 3). With reference to the ovary, it is well established that the anterior hypophysis is responsible for the initial maturation of ovarian follicles and their subsequent ovulation by virtue of its gonadotropic properties (4). The evidence also indicates that in rabbits these gonadotropic substances are discharged into the circulation from the anterior hypophysis in response to a reflex nervous stimulus (5, 6, 7). It seemed feasible, therefore, to make use of this sensitive physiological mechanism for determining whether or not the anterior hypophysis is under nervous control.‡ The sympathetic innervation of the anterior hypophysis is derived from the carotid plexus and consists of postganglionic fibers which emanate from the superior cervical sympathetic ganglion and terminate within the substance of the gland in intimate contact with its secretory epithelium (8, 9, 10). The present report is based on experiments in which the cervical division of these hypophyseal nerves was stim-

*Previous papers in this series have appeared in the American Journal of Physiology, 1916-1933.

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‡Studies by Cannon, his collaborators and others have demonstrated that under certain circumstances the functional activity of the thyroid gland can be increased by stimulation of the cervical sympathetic nerves. Evidence which has been cited to the contrary includes the facts that the thyroid gland functions normally in the absence of its nerve supply, and that the autonomic innervation of the thyroid gland is wholly vascular and not epithelial (Nonidez). The fact that the superior cervical sympathetic ganglion sends fibers through the carotid plexus to the anterior lobe of the hypophysis as well as directly to the thyroid gland may serve to reconcile these apparently irreconcilable views. During the past year, one of us (H. B. F.) at Dr. Cannon's suggestion, has been studying the histology of the thyroid gland and the basal metabolic rate of cats and rabbits after faradic stimulation of the cervical sympathetic nerves in order to determine whether the anterior hypophysis can be made to secrete its thyreotropic substance under such experimental conditions. This investigation, which is still in progress, indicates that there are transient irregular increases in metabolism after such stimulation. Quantitatively the response is limited and in this respect simulates the submaximal gonadotropic effects elicited from the ovary.

ulated faradically and the ovaries subsequently studied for evidence of those changes which are characteristic of anterior hypophyseal gonadotropic activity. The rabbit is particularly ideal for such experiments because it does not ovulate spontaneously (5, 11) and the ovaries of isolated unmated rabbits do not show maturation changes in their preovulatory follicles (Table 1).

TABLE 1

Rabbit	Duration of Stimulation (Bilateral) Hours	Hours Between End of Experiment and Autopsy	Preovulatory Follicles (1 ovary)	Mean* Diameter of Preovulatory Follicles Microns	Condition of Follicles and Ova
1S	½	24	1	1532	1 egg ovulated; 1 ovum with first polar body and second polar spindle; practically free from basal epithelium.
2S	1¾	26	4	1392	3 eggs ovulated; 1 unusually large atretic blood follicle; 4 ova with first polar body and second polar spindle; all preovulatory ova practically separated from basal epithelium.
8S	1	24	8	1190	1 egg ovulated; 8 ova with first polar bodies and second polar spindles; one of these with stigma on verge of rupture.
5S	3	48	3	1082	2 ova with first polar spindle; 1 with partly dissolved nuclear membrane.
6S	2½	42	5	1023	11 atretic blood follicles; in the 5 preovulatory follicles 2 ova had first polar body and second spindle, 2 had first polar spindle and 1 had tetrads and nuclear membrane dissolution.
7S	2	72	3	961	All with tetrads and beginning of nuclear membrane dissolution.
10C	0	24	4	1000	Nuclei of all ova vesicular.
11C	0	24	4	993	Nuclei of all ova vesicular.
12C	0	24	4	1245	Nuclei of all ova vesicular.
13C to 36C (23 animals)	0	..	160 2 ovaries	1021 (24 measured)	Nuclei of all ova vesicular.

Evidence of stimulation of the follicles and ova is characterized by the following phenomena in the normally mated doe:

1. The secondary liquor folliculi is secreted into the follicle, and the strands connecting the corona radiata to the basal follicular epithelium are gradually separated from their connections.

2. The ovum goes through a definite sequence of events in its maturation. The latter begins with the formation of tetrads within the nuclear membrane and proceeds in the order mentioned with dissolution of the nuclear membrane, the formation of the first polar spindle, giving off of the first polar body and finally the formation of the second polar spindle.

EXPERIMENTAL TECHNIQUE

Thirty-two adult female rabbits were isolated in separate cages for a period of 3 to 4 weeks before being used in the present investigation. Faradic stimulation of the cervical sympathetic nerves was carried out in 6 of these animals, while 3 of them (controls) were subjected to the same operative procedures up to but not including the stimulation of their cervical sympathetics. Just before operation each rabbit was given urethane

*The mean diameter is the average of the largest and smallest diameters, excluding the theca.

intravenously in doses of 0.6 gram per kilogram of body weight. This dose of urethane was sufficient to maintain a light anesthesia during the actual operative procedures, but its effects were largely dissipated before stimulation of the sympathetic nerves was started. The technique of oper-

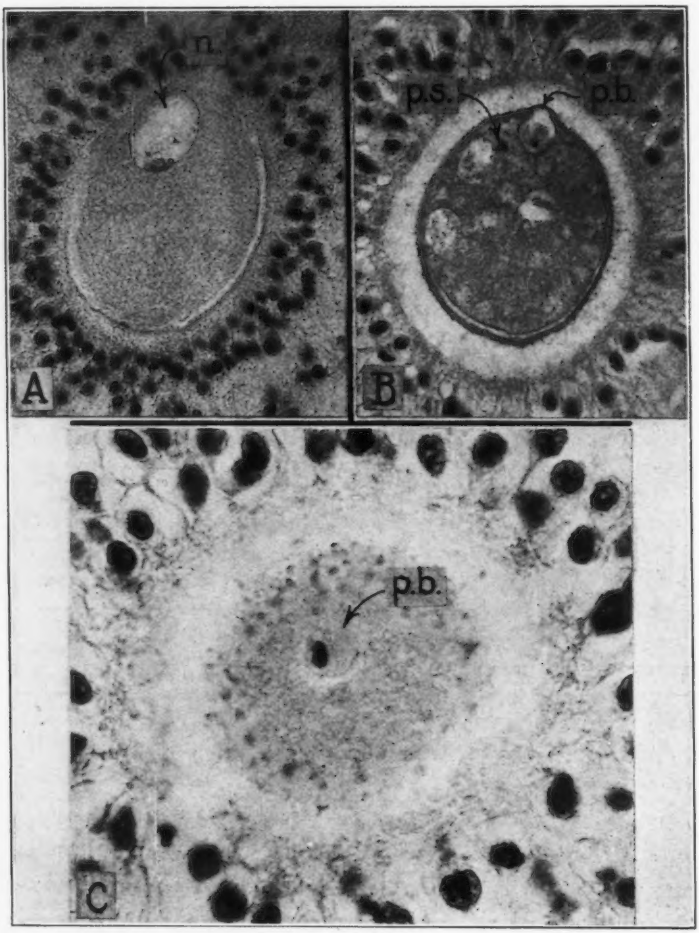

Fig. 1. A. No. 11C. Vesicular nucleus (n) at periphery of normal unstimulated ovum (x340).

B. No. 88. Stimulated ovum (x340) with first polar body (p.b.) and second polar spindle (p.s.).

C. No. 88. Oil immersion view of ovum (x770) during the process of ovulation (see Fig. 2B). First polar body (p.b.) lies near the center of the ovum in this plane, while the second polar spindle was found in an adjacent section.

ation was identical in all instances; and the 3 rabbits, which were used to control these studies, were left on the operating table after the routine dissection for approximately 2 hours, after which their operative wounds

were closed in the usual manner. These experiments were further controlled by examination of the ovaries of the other 23 unmated isolated rabbit does for microscopic evidence of ovum maturation.

The cervical sympathetic nerves of the 6 experimental animals were placed on silver wire bipolar electrodes which were insulated by rubber sheaths to prevent any spread of the stimuli. Each nerve was crushed or tied off at a convenient point between the electrode and the stellate ganglion before stimulation was started. The stimuli consisted of single shocks from a Harvard induction coil with 8 volts in the primary circuit. A mechanical interrupter delivered these shocks at a frequency of approximately 25 per second. The intensity of the stimulus was adjusted in each instance to produce maximal vasoconstriction in the ear. The nerves were stimulated bilaterally and simultaneously over periods ranging from 30 minutes to 3 hours; and stimulation was interrupted every 10 minutes for a rest period of 2 minutes.

Twenty-four to 72 hours after the end of stimulation the ovaries were removed, examined macroscopically and fixed in Bouin's solution. The fallopian tubes of all the does were washed with Ringer's solution and the washings thereof examined for ova. One ovary from each doe was sectioned serially to examine the contained ova for signs of stimulation, and the diameters of the preovulatory follicles were measured in each instance.

EXPERIMENTAL RESULTS

CONTROL EXPERIMENTS. None of the does in this series of controls ovulated; nor did microscopic examination of their ovaries reveal evidence of follicle stimulation. These controls were entirely negative in spite of the fact that the follicles in No. 12C were notably large, and the preovulatory follicles in all the controls contained ova with nuclei in the vesicular stage. The latter are characteristic of ova in the large follicles of unmated does on heat.

STIMULATION EXPERIMENTS. Bilateral stimulation of the cervical sympathetics resulted in positive evidence of a direct effect upon the functional activity of the anterior hypophysis and an indirect effect upon that of the ovary.

Time of Ovulation. Three of the 6 does actually ovulated; 1S showed 3 corpora lutea, while 2S had 1 corpus luteum. A corresponding number of ova were recovered from the fallopian tubes in each instance. The ovum from 8S was found at the point of rupture of the follicle in the act of being extruded. The 3 ova from 1S were massed together in the surrounding follicle cells, while the ovum from 2S was still surrounded by follicle cells and corona radiata. Ordinarily the ova from does with are mated with vasectomized male rabbits are surrounded by follicle cells for 6 to 8 hours after ovulation (12, 13). This implies that the ovulated ova of the does in this experimental series were dehisced from the ovary at least 16 hours after stimulation of the cervical sympathetics. However, judging by the condition of the corona and follicle cells, ovulation prob-

ably did not occur until 22 to 24 hours after cessation of stimulation. The period required for ovulation under these experimental conditions was therefore considerably delayed as compared with that for normally mated animals, which is 10 to 12 hours *postcoitum*. In this respect our data are

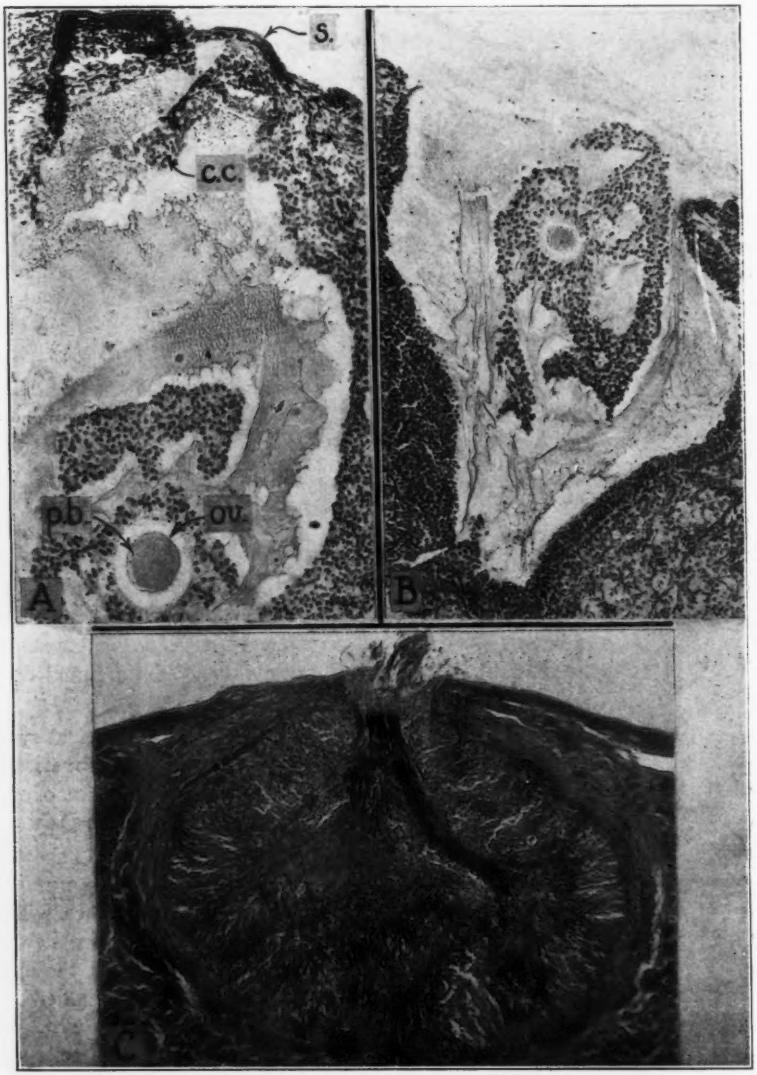

Fig. 2. A. No. 68. The arrow at "s" points to the stigma which is at the verge of rupture. Cumulus cells (c.c.) are to be seen at the crucial point, and the first polar body (p.b.) is visible within the ovum (ov.) (x125).

B. No. 88. Ovum (x90) in act of being dehisced during ovulation. For higher magnification of ovum see Fig. 1C.

C. No. 28. Follicle after ovulation (x70).

identical with those of Marshall and Verney (14), who studied the ovary after non-specific electrical excitation of the brain and spinal cord. The unlocalized character of their stimulus and the unknown areas which might have been stimulated preclude the possibility of drawing any pertinent conclusions concerning the mechanism responsible for the ovulation which they observed.

Extent of Ovarian Response. Evidence of ovarian stimulation was limited for the most part to signs of ovum maturation (15), although a limited number of follicles in 3 of the rabbits participated in ovulation. The mean diameters of the preovulatory follicles seemed to run parallel with the degree of ovum maturation (Table 1).

The stimulated follicles and ova of the animals in this series which did not ovulate resembled those of rabbits injected with subovulatory doses of anterior hypophyseal extracts (15). It is concluded, therefore, that faradic stimulation of the cervical sympathetic nerves resulted in the release of varying amounts of gonadotropic substance from the anterior hypophysis. As a result of this phenomenon, the ovulation threshold was exceeded in some of the animals; while in others the hypophyseal secretion was sufficient either to complete maturation of the ovum without ovulation or just enough to initiate maturation of the ovum without carrying this process to completion. These results also indicate that the cervical sympathetic fibers may carry at least some of the impulses which stimulate the pituitary to secrete its gonadotropic substances subsequent to coition.

DISCUSSION

Weed, Cushing and Jacobson (16) have reported that the sympathetic innervation of the posterior hypophysis is functionally active and that stimulation of the superior cervical sympathetic ganglion results in glycosuria. Keeton and Becht (17) ascribe their results to reflex stimulation of the adrenal glands, while Rabens and Lifschitz (18) believe that they may be attributed to prolonged anesthesia. For the most part, the reports in the literature concerning the anterior hypophysis also deny that the cervical sympathetics mediate impulses which can influence its functional activity. Nevertheless, Vogt (19) and Haterius (20) have found that pseudopregnancy in the rat does not occur as a result of mechanical or electrical stimulation of the cervix uteri after cervical or abdominal sympathectomy. To the contrary are their results (19, 20), which show that pseudopregnancy does occur after such sympathectomies if the females are mated with vasectomized males. The picture is still further complicated by the investigations of Hinsey and Markee (21) and Haterius (22), who have demonstrated that normally mated female rabbits ovulate and become pregnant in spite of cervical sympathectomy. It would seem, therefore, that ovulation under these experimental conditions is dependent upon another factor which is called into play during coition and which obviates the necessity of having an anatomically intact cervical sympathetic pathway. Observations by Brooks (29) also support this conclusion.

Haterius (22) has published the only direct proof which can be cited against the thesis which our observations have established; but the negative results which he reported after stimulation of the cervical sympathetics are probably due to his technique of stimulation. The rate at which faradic stimuli are sent into the cervical sympathetic nerves is of paramount importance. The maximal response by these nerves is obtained with approximately 20 stimuli per second, whereas excessive frequencies of stimulation such as Haterius employed are actually detrimental (23, 24, 25, 26, 27). Furthermore, the total duration of stimulation in our experiments is much longer than that used by Haterius. Our series is too limited, however, to determine whether or not this is a significant point of difference.

The ovarian changes which we observed after stimulation of the cervical sympathetics differed quantitatively, not qualitatively, from those obtained after normal mating. This submaximal response might have been due either to inadequate stimulation of the anterior hypophysis or to the physiological condition of the rabbit. Even the after-effects of the light urethane anaesthesia might have interfered with the intensity of the physiological response which was elicited. With reference to the adequacy of stimulation, it remains to be demonstrated whether faradic excitation of the cervical sympathetic nerves alone can result in sufficient pituitary activity to induce a high level of gonadotropic secretion. Similarly, it must be determined whether the apparatus used for stimulation is the most satisfactory which is available for that purpose. As for the condition of the rabbit itself, it is not possible to predict the intensity of the ovarian response in a given rabbit before its mating. When an attempt is made to mate a number of does, some of them, although apparently on heat, may refuse to mate; and about one in ten which does mate fails to ovulate. In either case their ovaries often show submaximal preovulatory follicles, and maturation changes may be found in the ova of the rabbits which do not ovulate after mating (Pincus, unpublished data). Although we purposely avoided testing the mating capacities of our rabbits, it is fairly certain that at least 2 of the does (6S and 7S) would not have ovulated on mating, or more likely, would not have mated at all. The ovaries from 7S contained only small preovulatory follicles such as are seen in animals off heat; while the ovaries from 6S showed 11 blood follicles (atretic), which indicated that the animal was practically off heat (5). In spite of such unfavorable conditions, the ovaries of both animals showed signs of stimulation, and 6S particularly revealed considerable evidence of advanced ovum maturation. There is also the distinct probability that some or all of the other does in this series were not completely on heat. During the course of the present investigation (July and August, 1935) an attempt was made to mate a total of 60 other does from the same colony of rabbits. Only ten successful matings resulted, although the attempt was made approximately three times with each doe. When a doe is not completely on heat, it is possible that the concentration of available gonadotropic sub-

stance is decreased to a point where the process of ovum maturation can occur, but that of ovulation is interrupted. That such a condition is physiologically possible is suggested by the work of Hinsey and Markee (28), who found that ovulatory doses of prolan initiated polar body formation but failed to cause ovulation in a large proportion of rabbits hypophysectomized more than 2 hours before injection of the prolan.

SUMMARY

Thirty-two adult female rabbits were isolated in separate cages for a period of 3 to 4 weeks before being used in the present investigation. Faradic stimulation of the cervical sympathetic nerves was carried out in 6 of these animals, while 3 of them (controls) were subjected to the same operative procedures up to but not including the stimulation of their cervical sympathetics. The remaining 23 rabbits (also controls) were sacrificed after their period of isolation.

None of the controls showed either ovulation or microscopic evidence of ovum maturation; whereas each of the 6 rabbits which had their cervical sympathetics stimulated revealed extensive maturation of their ova, and ovulation occurred in 3 of them (see Table 1).

It is concluded from these results that the rate of secretion of the gonadotropic principle can be experimentally increased by faradic stimulation of the sympathetic fibers which innervate the anterior hypophysis. These experiments also indicate that the cervical sympathetic nerves may be at least partially responsible during coition for stimulating the anterior hypophysis to release its gonadotropic secretions in increased amounts.

We are deeply indebted to Dr. W. B. Cannon for the advice and co-operation which made this investigation possible. We wish also to express our appreciation to Miss Ruth Ames for technical assistance with the histological preparations.

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Abstract Department

Some factors affecting adrenal insufficiency in the rat. Agate, F. J., Jr., and R. L. Zwemer, Am. J. Physiol. **111:** 1. 1935.

In 239 rats of four different strains the mortality rate after adrenalectomy carried out with rigid surgical technic was less than 10%. The same strains have been reported by others as having an 80 to 100% mortality rate. Incidence of survival is decreased by trauma, prolonged anesthesia, poor general health and inadequate diet. Changes in the gonads and in oestrous cycles after adrenalectomy in the rat may be due to adrenal insufficiency, but seem to be induced by factors other than the removal of both adrenal glands. Under optimal conditions neither fertility nor regularity of oestrous cycles was seriously affected. Loss of body weight is indicative of adrenal insufficiency, but does not necessarily occur after adrenalectomy of the rat. The results obtained with the adrenalectomized rat are not always comparable with those obtained in complete uncomplicated adrenal insufficiency.—R. G. H.

Some neurological aspects of suprarenal insufficiency. Cornwall, L. H., New York State J. Med. **33:** 642. 1933.

The neurological symptoms in three cases of suprarenal insufficiency were emphasized. In the first patient, a man of 32 years, sudden coma was the outstanding symptom. The systolic blood pressure remained above 100 mm. Hg. until shortly before death, when it dropped to 65 mm. Hg. Autopsy disclosed bilateral gummata of the suprarenal bodies. In the second patient, a woman of 21 years, profuse vaginal hemorrhage was the initial symptom. There was some improvement following transfusion but the development of somnolence, confusion, mild delirium and hyperthermia suggested the diagnosis of epidemic encephalitis. Examinations of the spinal fluid disclosed a low pleocytosis (11 and 12 cells) and a globulin excess on one occasion. The blood urea varied from 65-75 mg., the urinary findings being essentially normal. The systolic blood pressure remained above 100 mm. Hg. until the second week, when it gradually dropped to 65 mm. Hg. Death occurred on the seventeenth day and the autopsy revealed the absence of the right suprarenal body and atrophy of the left. In the third patient, a young girl of 14, spasmodic abdominal pain resembling gastric crisis was the prominent symptom and the increase of the creatine excretion (362 mg.) was emphasized as an important biochemical feature.—Author's Abst.

Tumors of the adrenal gland; a clinical report of two cases. Culver, H. and M. Davison, J. Urol. **32:** 428. 1934.

This is the report of a case of hypernephroma and one of ganglioneuroma successfully treated by removal of the tumors.—J. C. D.

Medullary hyperplasia of the adrenal and hypertension in old age (Hyperplasie medúllo-surrénale et hypertension chez le vieillard). Duthoit, A., Compt. rend. Soc. de biol. **112:** 1428. 1933.

Nine subjects with blood pressures of 210 to 300 were examined. All adrenals were large, 11 to 16 grams in weight. The medulla was enlarged in 7 of these cases, the cortex in 5.—J. C. D.

Histochemical localization of vitamin C in the adrenal cortex (Localisation histochimique de la vitamine C dans le cortex-surrénal). Giroud, A. and C. P. Leblond, Compt. rend. Soc. de biol. **115:** 705. 1934.

A histochemical study of the adrenal cortices of 40 rats and 20 guinea-pigs, based on the reduction of silver nitrate by "ascorbic acid," indicated a homogeneous distribution of vitamin C in the fascicular and reticular zones, and a lack of vitamin C in the zona glomerulosa. Reduction of silver nitrate occurred only in the cytoplasm of the cells.—J. C. D.

The rôle of adrenaline in the production of ventricular rhythms and their suppression by acetyl-B-methylcholine chloride. Hoff, H. E. and L. H. Nahum, J. Pharmacol. & Exper. Therap. **52:** 235. 1934.

From experiments on cats it was concluded that ventricular rhythms arise when the rhythmicity of some ventricular focus exceeds that of the pacemaker. In normal animals intravenous injections of adrenaline produce ventricular rhythms by increasing the rhythmicity of the ventricles while at the same time the rate of the pacemaker is decreased by the depressor reflex. Benzol, chloroform, and probably other factors, sensitize the ventricular myocardium to the adrenaline in the body, and this way so increase the ventricular rhythmicity that ventricular rhythms appear. These ventricular rhythms are readily abolished by acetyl-choline (acetyl-B-methylcholine chloride) in appropriate doses.—Author's Abst.

The nature of ventricular fibrillation following electric shock and its prevention by acetyl-b-methyl choline chloride. Hoff, H. E. and L. H. Nahum, Am. J. Physiol. **110:** 675. 1935.

Ventricular fibrillation in the cat was produced by electric current (110 v. A.C.) applied through electrodes on the right foreleg and left hind leg (10 experiments). While a shock of 3 seconds' duration usually produced ventricular fibrillation lasting for more than a minute and, but for artificial respiration and cardiac massage, led to death, such a shock after subcutaneous injection of 25 mg. of acetyl-b-methyl choline chloride was not followed by ventricular fibrillation (5 experiments). Effective beats of the heart were maintained, and respiration did not fail. Respiratory failure in such shocks in normal animals must therefore be secondary to circulatory failure. While after acetyl-b-methyl choline chloride ventricular fibrillation did not result from a shock, auricular fibrillation invariably did. In 4 experiments removal of stellate ganglia and adrenal glands markedly decreased the susceptibility of the heart to ventricular fibrillation following electric shock. Subcutaneous injection of adequate amounts of adrenaline restored the normal response to shock, and if greater quantities were injected in these or in normal animals, the danger of fatal ventricular fibrillation was greatly increased.—R. G. H.

Paroxysmal hypertension; blood pressure crises and tumor of suprarenal medulla (Parox smale Hypertension. Blutdruckkrisen und Tumor des Nebennierenmarkes). Kalk, H., Klin. Wchnschr. **13:** 613. 1934. Abst., J. A. M. A. **102:** 2152.

Kalk gives the history of a patient with a tumor of the suprarenal medulla which was successfully removed. In this case the blood pressure was not constantly increased. The hypertension occurred in attacks and the symptoms were limited to those traceable to the suprarenal medulla, the other incretory functions, with the exception of those of the parathyroids, being normal. The "counter regulation" with sudden decrease in blood pressure, redness of the face, contraction of the pupils, profuse sweating and salivation, which occurred at the height of the attacks, seemed to indicate the sudden elimination of a hormone antagonist of epinephrine. The author points out that cases of this nature may be more frequent than is generally thought and he thinks that perhaps cases of paroxysmal hypertension are due to tumors of this type. Moreover, it is possible that the so-called blood pressure crises (Pal) are often due to tumors, or at least to a hyperfunction of the suprarenal medulla.

Effect of salt treatment on certain changes following adrenalectomy. Kutz, R. L., T. McKeown and H. Selye, Proc. Soc. Exper. Biol. & Med. **32:** 331. 1934.

The dioestrus which follows removal of the adrenals in rats is probably not the result of the absence of any specific sex hormone found in the adrenal glands, but rather of the general ill-health of the animals.—M. O. L.

Muscular phosphagen following complete destruction of frog suprarenals (Le phosphagène musculaire après destruction totale des surrénales chez la grenouille). Moschini, A., Compt. rend. Soc. de biol. **115:** 215. 1934.

The suprarenal glands of 23 frogs were completely destroyed by means of a heated needle or an electric cautery. The survival period ranged between 2 and 5 days. Quantitative analysis of muscle phosphagen by Briggs' modifi-

cation of the Bell-Doisy method showed that muscles of suprarenalectomized animals contained between 30.2 and 4.0 mg. of phosphagen per 100 gm. of muscle as compared to the normal 50-55 mg. Phosphagen diminution was not pronounced until the onset of muscular asthenia.—J. C. D.

Hemorrhage and subsequent calcification of the suprarenals. Snelling, C. E. and I. H. Erb, J. Pediat. **6:** 22. 1935.

The authors discuss the records of 43 cases of suprarenal hemorrhage observed at post mortem. Only one case was diagnosed clinically. Fifteen of these were in the new-born and of the older age group, 15 were found associated with infection such as chronic renal disease, septicemia and meningitis. Four followed burns. Calcification was found in 6 cases in which death was due to intercurrent disease and in two in the new-born period. Calcification of the adrenals is not limited to tuberculosis of the gland but also occurs as a late manifestation of hemorrhage.—M. B. G.

Cortin protection against anaphylactic shock in guinea pigs. Wolfram, J. and R. L. Zwemer, J. Exper. Med. **61:** 9. 1935.

Studies have been made on a possible protective action of cortin in the prevention of anaphylactic shock induced by crystallized egg albumin. Of 16 control guinea pigs only 2 survived. Sixteen of 33 cortin-treated animals received hormone at the optimum period of from 2 to 6 hours before the shocking dose. Nine survived and 2 others showed some protection. In groups treated at other time intervals the evidence of protection is inconclusive. Two weeks after the first test the cortin-treated survivors succumbed to a second antigen dose, which was not preceded by cortical extract.—Authors' Summary.

Growth and development; the endocrine glands and growth. Aldrich, C. A., J. Pediat. **6:** 392. 1935.

The relationship between growth and development and the endocrine glands is discussed very fully in this chapter. Among the clinical entities of interest to the physician who treats children are dwarfism, giantism, pituitary cachexia, pubertas praecox, myxedema, adiposogenital dystrophy and eunuchoidism.—M. B. G.

The failure of roentgen-ray therapy of pituitary and adrenals in essential hypertension. Baird, P. C., J. R. Lingley and R. S. Palmer, New England J. Med. **211:** 952. 1934.

This gives the case histories of 8 patients suffering with severe hypertension. X-ray treatment over the pituitaries or adrenals or both was without favorable effect.—J. C. D.

The effect of a high fat meal on the respiratory quotient and heat production of normal and obese individuals. Bowen, B. D., F. R. Griffith, Jr., and Grace E. Sly, J. Nutrition, **8:** 421. 1934.

The possibility that a qualitative metabolic variation exists in the obese person is discussed. This variation from the normal is based upon the finding of a lower post-absorptive respiratory quotient in the obese subject. The effect of a large fat meal has been observed on 12 normal subjects, 6 of whom were slightly underweight, 20 non-diabetic obese and 11 obese diabetic subjects. The absorptive respiratory quotients indicate that the food mixture during this absorption is approximately the same in normal and obese persons. This response in the diabetic obese group suggests that less carbohydrate was being combusted during the utilization of fat. The observations were extended long enough to demonstrate the returning trend of the respiratory quotient to the post-absorptive level. No correlation between the curves of the absorptive respiratory quotients and the curves of the specific dynamic action could be demonstrated. A specific dynamic action of fat was present in all groups. It was found to be approximately the same in the obese and the normal people. This action, however, was considerably greater in the obese diabetic individuals.—Authors' Summary.

Xanthoma accompanied by hypercholesterolemia, occurring in an otherwise normal individual, and in an individual with acromegaly and diabetes. McGavack, T. H. and H. C. Shepardson, Ann. Int. Med. **7**: 582. 1935.

The incidence of xanthomatosis (excepting the Schuller-Christian syndrome and Niemann Pick's disease) is noted as recorded in the literature. Findings in one case of idiopathic disseminated xanthomatosis, and in one case of acromegaly with xanthoma diabeticorum, are recorded. In the non-diabetic individual, moderately restricted diet and thyroid gland administration were attended by a partial involution of the xanthomatous lesions. High cholesterol feeding for a short period (two weeks) did not affect the blood cholesterol level. Insulin administration had no obvious effect upon either the blood or cutaneous disturbance. In the acromegalic patient with xanthoma diabeticorum, administration of a high carbohydrate, low fat and low caloric diet with insulin, was accompanied by some lowering of the hypercholesterolemia and a diminution in the number and size of the skin nodules. Features of especial interest are noted: (a) the rarity of the condition exhibited in the second patient—association of acromegaly, diabetes mellitus and xanthoma diabeticorum; (b) the excessively high blood cholesterol value in both cases; (c) the low cholesterol content of the blood corpuscles despite very high plasma values. Some factors concerned in cholesterol metabolism and in the production of xanthoma are discussed with particular reference to the cases reported.
—Authors' Abst.

Prediction of basal metabolism from pulse pressure and pulse rate. Rabinowitch, I. M., Canad. M. A. J. **32**: 135. 1935.

It is possible to predict the rate of metabolism from pulse pressure and pulse rate with a reasonable degree of accuracy in about 50% of cases only. Under certain conditions the procedure may be useful, but it should not be employed when accurate direct determination is possible.—A. T. C.

Basal metabolism in children of normal and subnormal intelligence with blood cholesterol and creatinine values. Rothbart, H. B. and A. B. Haw, Am. J. Dis. Child. **49**: 672. 1935.

The investigations were carried out on 98 children of both sexes between the ages of 9.6 and 16 years. The intelligence quotients ranged from 60 to 120. The authors draw the following conclusions: (1) There is no definite relationship between the basal metabolism and the intelligence quotient. (2) The normal basal metabolism of boys ranged from minus 10 to plus 15 and of girls from minus 10 to plus 10. (3) There is no relationship between the cholesterol content of the blood and the basal metabolic rate. (4) There is no essential difference in blood cholesterol values between children of normal and retarded intelligence (I.Q. of 90 used as a dividing line). (5) The values of blood creatinine were between 1.2 and 1.6 mg. per 100 cc. for both sexes and are not related to the basal metabolism, cholesterol or intelligence quotients.
—M. B. G.

Mongoloid imbecility in the mongoloid races; report of two cases in Chinese children. Sweet, L. K., J. Pediat. 5: 352. 1934.

The case histories of two Chinese children with mongoloid imbecility are presented in detail. Three similar children, one a Eurasian, are mentioned. With the publication of this report there are recorded in the literature six definite instances of mongolism in Chinese and 60 or more in Japanese patients.
—M. B. G.

Disorders of internal gland secretion in children. Talbot, F. B., J. Pediat. **6**: 102. 1935.

In a critical review of the articles appearing in 1934, the author calls attention to the confusion resulting from the lack of standardization in nomenclature. Anderson advocates the use of diiodothyrine in myxedema on the supposition that it becomes converted into thyroxine. He has never observed toxic symptoms. The relative calorogenic action of several thyroid preparations is discussed by Lerman and Salter. In hyperthyroidism in children, Lahey calls attention to the dangers of removing too much of the thyroid, thus affecting growth and development. High cholesterol content of the blood is reported by several authors in hypothyroidism. Creatine excretion is diminished or absent in hypothyroidism. Interest is being focused upon the parathyroid gland, especially on hyperactivity, which may be diagnosed by calcium

and x-ray studies. The pituitary gland continues to hold an important position especially in the relationship to the thyroid and gonads. Good results in cryptorchidism are being reported with the use of anterior pituitary-like substances of pregnancy urine. Evidence is being accumulated that there is a relationship between the suprarenal cortex and some of the vitamins and also with schizophrenia. Hypertension due to hyperadrenalism is being treated by subtotal bilateral suprarenalectomy. Clinical studies on hyperinsulinism are being conducted in several clinics.—M. B. G.

Glandular physiology and therapy; the physiology of estrogenic principles. Allen, E., J. A. M. A. **104:** 1498. 1935. Abst., A. M. A.

The author stresses the following points in the physiology of estrogenic substances: First, as a major objective, the fundamental endocrine mechanism of the estrous and menstrual cycles has been demonstrated. Active hormones have been isolated and their relation to one another partially worked out. Second, incidental to the first point, the reaction of the rodent's vagina has provided a practicable test for the biologic standardization of therapeutic products, and these have now replaced the inert gland extracts previously in wide clinical use. Third, the extension of the test to carcinogenic substances and to other substances of similar chemical structure from a wide range of sources is extremely important. In description of some of the carcinogenic and estrogenic substances, the time interval required may be considerably greater than that required for the growth phase of the estrous reaction to theelin. The reasons for variations in the time of reaction are not clear. It is not yet known whether some of the related substances included under the term "estrogenic" will produce more than the vaginal growth reaction. Few of them have been tested as to value in replacing other phenomena of estrus or menstrual phenomena in primates.

Theelin content of pregnancy urine and placenta of the chimpanzee. Allen, E., A. W. Diddle and J. H. Elder, Am. J. Physiol. **110:** 593. 1935.

Considerable amounts of estrogenic substances (theelin and theelol) have been recovered from the urine of chimpanzees at various stages during pregnancy and also from placenta of two of these animals at full term.
—Authors' Summary.

Experimental studies on the gonadotropic hormone in epitheliomas of the cervix uteri (Recherches expérimentales sur l'hormone gonadotrope dans les épithéliomas du col utérin). Cornil, L. and A. Escarras, Compt. rend. Soc. de biol. **115:** 605. 1934.

Of 25 young rabbits injected with urine of patients suffering with epitheliomas of the cervix uteri 13 gave positive results, 7 doubtful, and 5 negative results. Positive results included hemorrhagic follicles and congestion of the uterus and tubes. Extra-genital epitheliomas gave negative results in 9 of 10 cases (one doubtful).—J. C. D.

Action of thallium in experimental animals. Cox, A. J., Jr., and Eleanor B. Rodgerson, Proc. Soc. Exper. Biol. & Med. **32:** 653. 1935.

White rats given large or small quantities of thallium over periods up to 9 weeks in length showed no abnormality of the estrual cycle or of the reproductive organs. The basal metabolic rate of guinea pigs did not change during administration of small or large doses of thallium, except for a rapid decrease shortly preceding death. These findings fail to support previous claims that thallium intoxication is characterized by alteration of endocrine function.
—Authors' Summary.

The occurrence in human blood of a water soluble substance producing the Allen-Doisy test (Ueber das Vorkommen einer wasserlöslichen, Allen-Doisy-Test gebenden Substanz im menschlichen Blute). Engel, P., Wien. klin. Wchnschr. **47:** 847. 1934.

The author describes a method for the preparation of an aqueous alkali-soluble substance from human blood which gives a positive response in the Allen-Doisy test. He studied the blood of 75 patients, 44 male and 31 female. Higher concentration of this substance is reported in the blood of children. In certain types of malignancies there is a higher concentration. The extract has

no effect on the uterus. The action is similar to an extract prepared from the pineal gland of cows, but its action is not as prolonged. The extract has no gonadotropic effect, and produces none of the effects characteristic of the male hormone.—S. A. Thayer.

The response of the gonads of immature pigeons to various gonadotropic hormones. Evans, H. M. and Miriam E. Simpson, Anat. Rec. **60:** 405. 1934.

Riddle has shown that, though sensitive to hypophyseal gonadotropic hormone, the testis of the immature pigeon or ring dove is unresponsive to pregnancy-prolan. Hormones found in urine and serum appear to differ among themselves in respect to this biological reaction, one example having been reported where a pronounced reaction of avian testis occurred. It seemed therefore important to investigate further the urinary gonadotropic hormones by this biological test. One hundred and fifty-six Silver King pigeons 30 to 33 days old were used in the study. Gonadotropic hormones studied were standardized in immature rats. It was found that avian testis is not a sensitive test object for hormone from pregnant mares; doses which gave minimal but definite effects in rat had no effect on avian testis. The hormone present in urine after menopause (three cases) did not stimulate avian testis though given at doses far above those minimal for the rat. This was equally true of urine from a case of embryonal carcinoma of the testis. Bird's testis did not respond to synergist, pregnancy-prolan or combinations thereof in vitro, i.e., did not show synergism, a phenomenon well shown by immature female rats. The reaction of the bird's testis does not parallel that of the rat's ovary as regards response to various gonadotropic hormones; the bird test should therefore be valuable in classifying hormones.—Authors' Abst., Wistar Bib. Service.

Variation of results obtained from experimental cryptorchidism in guinea-pigs, depending upon the mode of operation and location of the testis in the abdominal cavity (Variation des résultats obtenus par la cryptorchidie expérimentale chez le cobaye suivant le mode opératoire et la place occupée par le testicule dans la cavité abdominale). Foncin, A. R. (Mme.), Compt. rend. Soc. de biol. **115:** 860. 1934.

Experimental cryptorchidism of young and old guinea-pigs effected by suturing of the orifice of the external inguinal canal and resection of the scrotum resulted in complete degeneration of germinal tissue. In operations where the testes were reached by laparotomy and fixed to the anterior abdominal wall the germinal epithelium and structure of the testis were sometimes unaffected.—J. C. D.

Experimental ovulation and the resulting pseudopregnancy in anoestrous cats. Foster, M. A. and F. L. Hisaw, Anat. Rec. **62:** 75. 1935.

The average number of ovulation points in the cat after normal copulation is four (Longley). In experimental ovulation of 37 cats the average number of points has been 12, with many individuals having over 30 each. Under normal conditions intravenous injection of A.P. extract will induce ovulation in cats only during reproductive phases characterized by large follicles (2 mm. in diameter), i.e., oestrus, late prooestrus and late pregnancy. In these experiments immature, anoestrous and cats in the first half of pregnancy have been used. Follicular growth was necessary before ovulation could be obtained. Several different pituitary extracts have been used for inducing follicular growth, but only the follicle-stimulating fraction has given constant follicular enlargement without atresia or hemorrhage. After follicular growth had been procured, an ovulating dose was administered intravenously. The follicle-stimulating fraction and the luteinizing hormone, separately and in combination, were used for intravenous injections. Optimal results were obtained with follicle-stimulating hormone plus small amounts of the luteinizing hormone. Other factors in experimental ovulation than those of pituitary hormone balance used follicular size and time of injection. In either case over-stimulation of the granulosa by increased dosage or prolonged injection results in injury which invalidates the ovulation response. Certain aspects of the cycle were also studied, especially those concerned with the lutein phase. After experimental ovulation a pseudo-pregnant state existed for approximately 35 days.
—Authors' Abst.

The absorption of estrogenic substances of pregnant urine administered orally to young rats. Freudenberger, C. B. and P. M. Howard, Anat. Rec. **60:** 267. 1934.

In order to determine whether the hormones of pregnancy urine are absorbed when administered orally such urine was administered to immature rats. The urine used was from women who were in the last half of pregnancy. Nine litters containing a total of 35 rats were used. It was found that the oral administration of the urine caused a premature opening of the vagina. Since the urine was often given in amounts not exceeding 0.1 cc., it is concluded that the hormones are absorbed directly from the oral mucous membrane. In an ovariectomized rat 0.075 cc. of pregnancy urine (diluted with distilled water) administered orally caused the premature opening of the vagina. This indicates not only that the estrogenic substances of pregnancy urine are absorbed well from the oral mucosa but that they are present in urine in very large amounts.—Authors' Abst.

The effect of theelin on the mammary rudiments of male mice differing in susceptibility to tumor development. Gardner, W. U., A. W. Diddle, E. Allen and L. C. Strong, Anat. Rec. **60:** 457. 1934.

Thirteen young male mice of each of three strains, in which the incidence of spontaneous mammary tumors in the female varied greatly, were injected with theelin for periods of from 15 to 147 days. Most of the animals were treated for 135 days or more. Three additional male mice of each strain were used as controls. The amount of theelin injected daily into the different animals varied from 1 to 5 rat units. The mammary glands of male mice normally remain rudimentary throughout life. These rudiments responded readily to theelin in all the dosages used. The duct system of the glands progressively developed for 60 to 75 days, thereafter persisting throughout the experiment, though occasionally showing evidence of a slight regression. No strain variations in rate or extent of mammary duct growth were observed. Some of the mammary rudiments had either failed to differentiate in embryonic development or disappeared later, as in no case was the expected number of glands found, even after prolonged stimulation. In three males of one of the tumor susceptible strains localized, atypical growths appeared which histologically resembled functional lobules. Theelin was thus capable of inducing in addition to the growth of the duct system localized alveolar development in at least this strain of mice.—Authors' Abst.

Testing the male sex hormone with fishes (Testierung von männlichem Sexualhormon mit Fischen). Glaser, E. and O. Haempel, Klin. Wchnschr. **12:** 1491. 1933.

Certain secondary sex characteristics can be influenced in both sexes either by the male or the female sex hormone. One of these is the growth of the ovipositor of the female bitterling. To test the effect of the different sex hormones, the authors made the following experiment. In each of 4 aquariums of the same size containing 5 litres of water they kept 6 bitterlings—3 males and 3 females. They added to the aquariums on 4 consecutive days the following sex hormones: 150 M.U. of female sex hormone (Hogival) to the first one; 200 Fish U. male sex hormone (Testosanforte) to the second one; 100 R.U. of anterior pituitary hormone (Praepitan) to the third; and 5 International U. of the posterior pituitary hormone (Pituisan) to the fourth. The males did not show any changes during the tests. The females were measured every day, especially for the growth of the ovipositor. At the end of a seven-day observation period it was found that female sex hormone had the greatest effect on the growth of the ovipositor; the male sex hormone was a little less efficient than the female. Both pituitary hormones gave a stimulus in this respect, although much smaller than the sex hormones.—G. L. Banay.

Prolongation of pregnancy in the rat by the injection of human pregnancy urine extract. Hoopes, Edith C. and Jessie L. King, Am. J. Physiol. **111:** 507. 1935.

In 31 rats it was found that pregnancy can regularly be prolonged for 3 or more days by one injection of 75 rat units of human pregnancy urine extract (antuitrin-S), given on the 19th or 20th day of gestation. Parturition was delayed until the 25th, 26th or 27th day and was also prolonged over 2 or more days. Fetuses remained alive and continued to grow for 2 or 3 days

beyond term. Necrosis of retained fetuses began after the 26th day. This was indicated by a mucoidal, blood-stained discharge from the vagina. Histological examination of the ovaries revealed induced corpora lutea by the 21st day of pregnancy, but subsequent retrogression of these could not be definitely established by the method used. The induced corpora lutea are regarded as taking over the function of those of pregnancy and their secretion as delaying the onset of labor. Vaginal smears suggesting a tendency to estrus were observed as early as the 27th day and even with fetuses in utero.—R. G. H.

Special position of tubular ovarian blastomas (arrhenoblastomas) as regards morphology and hormone function (Die morphologische und hormonalfunktionelle Sonderstellung der tubulären Ovarialblastome [Arrhenoblastome]). Kleine, H. O., Arch. f. Gynäk. **157:** 410. 1934. Abst., J. A. M. A. **103:** 1266.

Kleine points out that 35 cases of arrhenoblastomas of tubular structure have been reported thus far. Among the 4 cases that he observed was one in which there were dermoid cystomas in the other ovary. The growth of these tumors had begun at the hilus. Leydig's interstitial cells were demonstrable in all tumors. All patients exhibited more or less characteristic signs of virilism (psychic changes, altered body contours and changes in the hair growth and in the voice). In one patient the rete ovarii of the other ovary was considerably enlarged but was free from tumor cells. The development of a post-operative hyperthyroidism in one of the patients indicates the possibility of a pluriglandular disturbance. Reasoning along the lines suggested by R. Meyer, the author thinks that the parent tissues of the arrhenoblastomas are the rete ovarii, the medullary strands and the so-called extraglandular interstitial cells. These three epithelial formations represent heterosexual cell complexes of the ovary, which are present in small amounts in every ovary. The hypoplasia of the isosexual gonadal parenchyma seems to promote the development of the heterosexual tissues. The observations of other authors (R. Meyer) on younger women with arrhenoblastoma, in whom signs of virilism appeared simultaneously with the growth of the tumor, disappeared after extirpation and reappeared in case of relapse, prove a causal, incretory connection between these tumors and virilism. The author shows that three problems have yet to be solved: (1) the significance of the rete testis and of Leydig's interstitial cells for the development of the secondary male sex characters, (2) the problem whether arrhenoblastomas form a testicular incretion, and (3) whether there are relations between arrhenoblastomas and the suprarenal system.

Some influences of oestrin on the hypophyseal-gonad complex of the immature female rat. Lane, C. E., Am. J. Physiol. **110:** 681. 1935.

Follicle counts were made of the ovaries from 29 oestrin-injected rats and 22 uninjected controls and similar counts of the ovaries from 17 experimental pituitary recipients and 17 control pituitary recipients. Six and one-quarter rat units of oestrin per day were injected for periods ranging from 5 to 39 days. The pituitaries of the oestrin-injected rats were then implanted into normal 22-day-old rats and the recipient's ovaries also studied. From an analysis of the counts the following conclusions may be drawn: Injection of oestrin at first stimulates the hypophysis to liberate gonadotropic hormones in excess of those produced by normal animals. There is then an inhibition of the liberation of the follicle-stimuating hormone and there is apparently a failure of formation of this hormone a few days later. Oestrin causes a greatly enhanced formation and secretion of either the luteinizing hormone from the hypophysis, or of something associated with it, as seen in extracts, which acts in a similar way upon the ovary.—R. G. H.

Estrogenic hormones and carcinogenesis. Loeb, L., J. A. M. A. **104:** 1597. 1935. Abst., A. M. A.

The author discusses the three lines of investigation, conducted more or less independently of one another for a number of years, that have led recently to the conclusion that a remarkably close relation in chemical constitution as well as in biologic effects exists between estrogenic hormones and certain hydrocarbons that occur in tar and are able to induce cancer. The conclusions are that carcinogenic hydrocarbons of tar and related compounds, estrogenic substances as well as certain other factors, in the course of time may induce cancer formation in those tissues on which they act. But while carcinogenic hydro-

carbons as well as regenerative processes (irritation) may affect a great variety of tissues, the estrogenic hormones are limited in their action to the tissues in which they induce growth processes during the normal sexual cycle. Both carcinogenic hydrocarbons and ovarian hormones bring about the cancerous transformations of tissues in an indirect manner; they differ in this respect from other agents merely from a quantitative point of view. The mechanism by which ovarian hormones produce proliferative processes in the sex organs differs from the mechanism underlying the cancerous transformation, although the latter may ultimately depend on proliferative processes acting over a long period of time. There exist, therefore, no direct but only indirect connections between the carcinogenic action of the hydrocarbons of tar and the carcinogenic effect produced by estrogenic hormones.

The functional changes of the gonads under the influence of the toxins acting on the nervous system. Makarova, S. O. and G. V. Tutayev, Acta endocrinol. ucrainica, Pp. 34-35. 1934.

An investigation of choline stimulation (via the vagus nerve) on ovarian function was made on normal and castrated white mice and controlled on other young animals. It was found that choline inhibits the development of the oestral cycles in healthy mice and stimulates the action of menformon in castrated mice. It inhibits the development of the gonads in young animals. The addition of small quantities of menformon is sufficient to stop the inhibitory influence of choline on the development of gonads in young animals. Large doses of choline inhibit ovarian function. As choline is periodically accumulated and excreted, it may be considered as one of the regulating factors of the oestral cycle in adult animals.—M. Breitmann.

Prolan in the treatment of abnormal uterine bleeding. Meigs, J. V., New England J. Med. **211:** 289. 1934.

Fifty-nine patients suffering from various forms of abnormal bleeding were given 500 to 1000 rat units of prolan over a period of 10 days. In 54% there was definite improvement. The age group from 20 to 40 responded best. This therapy was not universally effective but avoided recourse to more drastic measures in a sufficient number of cases to warrant its trial.—J. C. D.

Atypical growth induced in cervical epithelium of the monkey by prolonged injections of ovarian hormone combined with chronic trauma. Overholser, M. D. and E. Allen, Surg., Gynec. & Obst. **60:** 129. 1935.

Atypical epithelial growth in the cervix uteri of 4 ovariectomized monkeys was experimentally produced. The changes consisted of marked squamous epithelial down growth, overgrowth and epidermization of the cervical glands in the region of the junction of the stratified squamous with the columnar epithelium. The treatment these animals received was as follows: Monkey 1 received 5,490 rat units of estrin in 90 days, with repeated cervical trauma. Monkey 2 received 1,660 rat units of estrin in 20 days, with repeated cervical trauma. Monkey 3 received 4,747.5 rat units of estrin and 14 cubic centimeters of corpus luteum extract in 81 days with repeated cervical trauma. Monkey 4 received 2,802.5 rat units of estrin and 10.7 cubic centimeters of corpus luteum extract in 84 days. This animal did not receive cervical trauma and the changes were very pronounced, the epithelial cells being very atypical. In 3 monkeys the results were practically negative possibly due to the following reasons: (1) injection period too short; (2) sloughing of epithelium from severe infection; (3) sloughing of epithelium from infection and from stopping hormone injections 42 days before sacrificing animal. A normal control receiving trauma only showed a slight amount of epidermization of cervical glands. An ovariectomized control receiving trauma only was completely negative.—Authors' Summary.

Action of ovarian follicle hormone in ovarian insufficiency in women as indicated by vaginal smears. Papanicolaou, G. N. and E. Shorr, Proc. Soc. Exper. Biol. & Med. **32:** 585. 1935.

Ovarian follicular hormone in oil, in dosage of 100 to 2000 rat units per day was given subcutaneously to 15 women with ovarian insufficiency following bilateral ovariectomy or menopause. There were produced increased

vaginal secretion; a gradual replacement of the epithelial cells characteristic of these conditions by squamous cells, largely cornified with small pyknotic nuclei; and a relative or absolute leucopenia. The effects were slightly cumulative and disappeared within a few days after treatment was stopped. Subjective improvement occurred.—M. O. L.

Studies in human physiology, urine chemistry; composition of 24-hour and short-period, basal excretion; correlations between urine constituents and menstrual and seasonal variation. Pucher, G. W., F. R. Griffith, Jr., K. A. Brownell, J. D. Klein and M. E. Carmer, J. Nutrition, **7**: 131. 1934.

Twenty-four-hour and short-period, basal, morning urines obtained once and twice a week from two men and three women over periods of 1 and 2 years were analyzed for the principal nitrogenous components, sugar, phosphate, chloride, organic, total acid. Coefficients of variation provide comparison of the relative constancy of excretion of these urinary components (1) with respect to each other; (2) with respect to other functions described in previous reports of this series. Coefficients of correlation established the interrelationship between (1) the urinary constituents themselves; (2) between them and simultaneous variations of basal metabolic rate. Menstruation: (1) accompanied by diminished excretion of most of the nitrogenous components, sugar, chloride, volume; (2) ammonia, acid, phosphate excreted minimally toward middle of intermenstrual period. (1) correlates positively with basal heart and metabolic rate and (2) inversely with alkali reserve, as previously described. No apparent seasonal variation for most components of 24-hour urines. Basal excretion for most minimal in late summer-early fall, paralleling previous findings for weight, basal heart and metabolic rate. Ammonia and acid of both types of urines are, on the other hand, minimal in spring, maximal in later summer-fall, as were similarly pulmonary ventilation, previously, and most blood constituents, later, to be described.—Authors' Abst.

Urinary excretion of oestrin administered under experimental conditions and after the menopause. Robson, J. M., T. N. MacGregor, R. E. Illingworth and N. Steere, Brit. M. J. **1**: 888. 1934. Abst., J. A. M. A. **103**: 220.

The experiments of Robson and his associates demonstrate that when ketohydroxestrin is injected intramuscularly into the ovariectomized human female or subsequent to the menopause only a small proportion of the hormone can be recovered in an active form from the urine by the methods used. The result is confirmed by experiments in which urine was injected into ovariectomized mice without any previous treatment; for although the toxicity of the urine rendered an accurate assay impossible, yet it could be definitely established that the quantities were comparatively small. The results indicate that the human body can rapidly destroy, or at any rate render inactive, the estrous hormone, and this view is supported by the finding that, four hours after the injection of 10,000 mouse units, the blood contained less than 25 mouse units of the hormone per liter.

New clinical sign of folliculin activity; tests of breasts (Un nouveau signe clinique de l'activité de la folliculine; le test des seins). Sauphar, G., Rev. franç. de gynéc. et d'obst. **29**: 496. 1934. Abst., J. A. M. A. **103**: 222.

Sauphar states that congestion of the breasts occurs almost constantly after the injection of a known dose of folliculin. It lasts a limited time and disappears without other symptoms, having provided a striking sign of the activity of the preparation employed. He observed that the results were more constant when an ester salt of folliculin, such as the benzoate, was used in place of the crystallized folliculin. In the second part of his work a preparation of dihydrofolliculin was therefore substituted for crystallized folliculin. The author believes that the benzoate of folliculin in single injection is the most active preparation; dihydrofolliculin administered orally in divided doses and crystallized folliculin orally give more inconstant results. Eight cases are reported showing this congestion of the breasts subsequent to the administration of the folliculin, since resistance apparently occurs with the passage of time. Finally he states that congestion of the breasts is a single clinical phenomenon from which no conclusions can be drawn other than the activity of the preparation introduced. The positive breast sign probably indicates dosage considerably in excess of that necessary therapeutically.

Isolation of corpus luteum hormone (Reindarstellung der Hormone aus dem Corpus luteum). Slotta, K. H., H. Ruschig and E. Fels, Ber. d. deutsch. chem. Gesellsch. **67:** 1270; 1624. 1934.

In these two notes the authors describe the isolation from corpus luteum extracts of a series of sterols, two of which ("Luteosteron C" and "Luteosteron D") are biologically active, and are believed to be stereoisomeric forms of a diketonic phenanthrene derivative having the formula $C_{21}H_{30}O_2$. The claim is made that both are necessary to give the "Corner-test" for progestin action, namely, progestational alteration of the rabbit's uterus, the optimum combination being 60-70% of substance C with 40-30% of substance D.

—G. W. Corner.

Remarks on synchorial litter mates in a cat. Wislocki, G. B. and G. W. D. Hamlett, Anat. Rec. **61:** 97. 1934.

An instance of fusion of the membranes of two cat fetuses (synchorial litter mates) is described together with the differential diagnosis from polyembryony. Although the fusion of the synchorial litter mates is extremely intimate, a hormonal effect of the male fetus upon the reproductive tract of the female partner (freemartin) or vice versa is not demonstrable. The present findings do not lend weight to the hypothesis that sterile male tortois-shell cats may be sex-inverted females, transformed by a hormonal influence resulting from the union of the membranes of two litter mates.

—Authors' Abst., Wistar Bib. Service.

Experiments with injections of anterior hypophyseal extract into the foetus of the guinea pig in utero. Action on the thyroid (Expériences d'injections d'extrait préhypophysaire au foetus de cobaye in utero. Action sur la thyroïde). Aron, M., Compt. rend. Soc. de biol. **113:** 446. 1933.

Such injections stimulate the foetal thyroid to overactivity as do injections in guinea pigs post partum.—J. C. D.

The thyroid and diuretic action of extract of the anterior hypophysis (Thyroïde et action diurétique de l'extract anté-hypophysaire). Biasotti, A., Compt. rend. Soc. de biol. **115:** 329. 1934.

Bovine anterior lobe extract injected intraperitoneally, produced marked diuresis in normal, but not in thyroidectomized dogs. The conclusion was that the extract acted indirectly through the thyroid.—J. C. D.

Size relationships as influenced by pituitary rudiment implantation and extirpation in the urodele embryo. Blount, R. F., J. Exper. Zoöl. **70:** 131. 1935.

Amblystoma larvae developing under the influence of a continuous, although experimentally produced, natural excess of immature pituitary tissue have their size relationships profoundly altered. This is also true of hypophysectomized individuals. In these experiments the excess pituitary tissue has resulted from the differentiation of additional anlagen transplanted during the embryonic period (Blount, 1932). These changes have been shown by a study of 27 different measurements made at 5-day intervals from before feeding to just before metamorphosis. The rates of growth have been determined and the importance of the measurements in body proportions evaluated by their ratios to the trunk length. For comparison the changes normally undergone in the growth pattern have also been worked out. As measured by total length and by volume the triple pituitary animals, and to a lesser degree the hypophysectomized donors, are greatly reduced in total growth. The peripheral integumentary parts such as gill length and caudal fin height are greatly reduced in the triple pituitary hosts, but are increased in the hypophysectomized individuals. Body parts which are largely skeletal, are normal in proportion although small in the hypophysectomized donors, but in the triple pituitary hosts such parts are disproportionately reduced. The growth of certain parts such as greatest head width and eye diameter are nearly heterogonic in character for the hypophysectomized donors after 25 days.—Author's Abst., Wistar Bib. Service.

A case of diabetes insipidus. Canelo, C. L. and H. Lisser, California & West. Med. **42:** 1. 1935.

A case of diabetes insipidus of 18 years' duration, which developed during convalescence from typhoid fever, is herein reported. Powdered posterior

lobe pituitary substance as a snuff and pituitrin hypodermically controlled the symptoms equally efficiently. Amidopyrin failed to relieve the patient. The literature on the treatment of diabetes insipidus is reviewed briefly.
—Authors' Summary.

Relation between the hypophysis and sexual organs of fishes (Relations entre l'hypophyse et les organes sexuels chex les poissons). Cardoso, D. M., Compt. rend. Soc. de biol. **115:** 1347. 1934.

Injections of fresh hypophyseal extract into fishes (Pimelodus clarias) (number not stated) produced a marked increase in the size and weight of the gonads.—J. C. D.

Gonad-stimulating or thyroid-stimulating action of the hypophysis of adrenalectomized rats (Pouvoir gonadostimulant ou thyréostimulant de l'hypophyse du rat surrénoprive). del Castillo, E. B., Compt. rend. Soc. de biol. **115:** 317. 1934.

Forty-eight rats were adrenalectomized, and at various intervals some were sacrificed, and their hypophyses were transplanted intramuscularly into normal young rats. In some cases salt suspensions of the hypophyses were injected intraperitoneally into young guinea-pigs. The mean weights of the ovaries and uteri of the rats which received hypophyseal transplants did not differ significantly from mean normal weights, and the mean weight of the thyroids of injected guinea-pigs was normal. Bilateral adrenalectomy did not produce histological variations in the hypophyses. It was concluded that ablation of the adrenals did not affect the gonad- or thyroid-stimulating action of the hypophysis.—J. C. D.

The anterior hypophysis of sheep and the melanophore reaction (La préhypophyse du mouton et la réaction des mélanophores). Collin, R. and P. L. Drouet, Compt. rend. Soc. de biol. **115:** 161. 1934.

The authors oppose the view of Popa and Fielding that the melanophore dilating principle originates by lysis of blood through fermentive action of the anterior lobe. They observed melanophore dilation in frogs 10 minutes after implantation of fragments of sheep anterior pituitary.—J. C. D.

Irradiation of the pituitary in arterial hypertension (Rôle de l'hypophyse dans l'hypertension artérielle. Bons résultats de la radiothérapie). Drouet, P. L., Bull. et mém. Soc. méd. d. hôp. de Paris, **50:** 139. 1934. Abst., Brit. M. J. No. 3826. 69.

The author describes two cases in which a lasting reduction in blood pressure followed x-radiation of the hypophysis. Both patients were females. One had symptoms of hyperthyroidism and the other had been castrated. Signs of posterior hypophyseal hyperfunction were present, it was thought, in (1) the demonstration of a melanophorotropic hormone in the urine, (2) the visual fields—one patient had very marked retraction of the fields for red and green, the other contracted field for white on one side and for red and green on both. Druet quotes the finding of Cushing that hypersensitive subjects may have pronounced basophilia of the pituitary pars nervosa.

The adrenotropic substance of the hypophysis as influenced by age, castration, sex and thyroparathyroidectomy. Emery, F. E. and C. A. Winter, Anat. Rec. **60:** 381. 1934.

A study was made of adrenal hypertrophy produced by pituitary implants or extracts in about 100 rats. The hypertrophy was not obtained in rats under 30 days of age, but in older rats 3 to 24 months old, age was not a factor in determining the amount of hypertrophy. That sex of the donor is an important factor in determining the amount of adrenal hypertrophy in the recipient is shown by the fact that a greater effect was obtained with pituitaries from female rats, guinea pigs, and cattle than with pituitaries from males. Castration of the donor has no appreciable effect on the degree of adrenal hypertrophy obtained. No hypertrophy was obtained in thyroparathyroidectomized recipients.—Authors' Abst.

The effect of posterior pituitary substance on the mineral balance (Untersuchungen über den Mineralhaushalt nach Zufuhr von Hypophysenhinterlappensubstanz). Engel, R., I. McQuarrie and Mildred Ziegler, Arch. f. exper. Path. u. Pharmakol. **173:** 248. 1933.

A study of the effect of the posterior pituitary substance (pitressin) on mineral balance was made. Na, K, Ca, Mg, Cl, P, S and N were determined in the urine and stools of one normal subject and four epileptics. The periods of observation varied from six days to two months. The most interesting feature regarding mineral exchange was the variations in Na and K. During periods of negative water balance and freedom from seizures, the excretion of Na in the urine exceeded that of K. There was also a negative balance of Cl as well as Na in K. During periods of positive water balance when seizures were more frequent, the K excretion predominated. The elimination of Ca, Mg, P, S and N was uninfluenced.—Mildred Ziegler.

Clinical manifestations of dysfunction of anterior pituitary. Evans, H. M., J. A. M. A. **104:** 464. 1935. Abst., A. M. A.

The author states that the experimental biology of the last decade, which has been directed toward securing both overfunction and underfunction of the pituitary gland, has now finally given adequate grounds for belief in the existence of at least five separate internal secretions or hormones of the anterior pituitary: the somatotropic, the gonadotropic, the thyrotropic, the mammotropic and the interrenotropic hormones. He feels that the relation of these achievements to clinical medicine will be disclosed most successfully by the discussion of pituitary and related diseases with reference to the existence of proved deficiency or excess of these five known substances, for the recognition of which there are now specific tests. The phases of the subject discussed pertaining to the separate hormones are: dwarfism, deficiency of growth hormone in adult life and gigantism and acromegaly, pregnancy, parturition, hydatidiform mole and chorionepithelioma, testicular tumors, castration, hypogonadism and the menopause, genital cancer, miscellaneous conditions with increased hormone, the function of the lactogenic hormone, the underproduction and overproduction of thyrotropic hormone, hypopituitary and hyperpituitary states, hypercortical and hypocortical states and carbohydrate, fat and protein metabolism.

The posterior hypophysis. Geiling, E. M. K., J. A. M. A. **104:** 738. 1935. Abst., A. M. A.

The author in his discussion of the posterior hypophysis, gives the primary structural elements of the posterior lobe of the hypophysis as the neuroglial cells, the pituicytes and the nerve fibers. The neuroglial cells resemble those found elsewhere in the central nervous system. In the pituitary some of them have become differentiated to form pituicytes, highly branched cells that have granules in the cytoplasm. The presence and significance of nerve fibers in the posterior lobe are still an open question. None of these structures, with the exception perhaps of the pituicytes, are regarded as secreting elements in the ordinary sense. He discusses the origin and path of escape of the secretion, the chemistry of posterior lobe extracts, the physiologic, cardiovascular, metabolic, respiratory, renal (diuretic-antidiuretic action) and oxytocic effects, the action on the intestine, clinical uses and the diseases ascribed to hypersecretion. He concludes that in spite of the huge volume of work on the posterior lobe secretion one cannot assign with certainty any specific physiologic rôle in the animal economy to this potent autopharmacologic agent. Possibly the pressor component acts as an efficient regulator of the exchange of metabolites between the blood and the tissues (capillary hormone) and exercises a renal function, and the oxytocic portion may function during parturition to quicken and render more effective the uterine contractions, which result in the expulsion of the products of conception.

Antuitrin-S effect upon blood elements. Geist, S. H. and F. Spielman, Proc. Soc. Exper. Biol. & Med. **32:** 353. 1934.

In 6 patients with functional uterine bleeding, injections of antuitrin-S three times weekly for 2 or 3 weeks had no significant effect upon blood hemoglobin, erythrocytes, white cells, platelets or coagulation time. The patients showed no improvement from the standpoint of bleeding.—M. O. L.

Polyglobulia with or without erythrosis in certain syndromes of the hypophysis and tuber cinereum (La polyglobulie, avec ou sans erythrose, de certains syndromes hypophysotubériens). Guillain, G., P. Lechelle and R. Garcin, Ann. de méd. **31:** 100. 1932. Abst., Arch. Neurol. & Psychiat. **32:** 1084.

Three cases of dystrophia adiposogenitalis and one case of acromegaly are reported in which the number of red blood cells was higher than 6,000,000 per cubic millimeter. In the last case the blood picture returned to normal after removal of a hypophyseal adenoma. Based on personal observations and other reports of polycythemia (type Geisböck), combined with erythermia, obesity, polyuria and disturbances of growth, the authors advance the hypothesis of the existence of a center for the regulation of the hematopoietic equilibrium in the subthalamic region.

The Golgi apparatus in relation to vacuolation in the basophiles of the anterior pituitary of castrate and of cancerous rats. Guyer, M. F. and Pearl E. Claus, Anat. Rec. **61:** 57. 1934.

The vacuoles of the hypertrophied basophile cells found in the anterior lobe of the pituitary of cancerous and of castrate rats have every appearance of being derived from the Golgi apparatus. Appearing at first as series of small, clear, highly refractive granules or droplets within the individual strands or walls of the Golgi body, after extrusion these hyaline bodies swell and coalesce into larger masses which finally fuse apparently to form the less highly refractive substance of the vacuole.—Authors' Abst., Wistar Bib. Service.

Necessity for caution in therapeutic use of preparations of anterior lobe of hypophysis (Vorsicht im therapeutischen Gebrauch von Hypophysenvorderlappenpräparaten). Hofbauer, J., Zentralbl. f. Gynäk. **56:** 1032. 1932.

Caution is necessary in the use of the preparations of the anterior lobe of the pituitary, which contain the growth hormone, especially in cases with hypofunction of the ovaries. In the preparations, which are made from the urine, the growth hormone is apparently missing. The preparations made from the placenta should first be investigated for the presence or absence of the growth-producing hormone, before it is used for therapeutic purposes. Two illustrations show the increase in size of the kidneys and heart of a guinea pig in which a transplantation of fresh cattle pituitary was carried out four times after both ovaries were removed. The guinea pig died in about two weeks, suddenly. Similar, but less marked, changes were found in other animals kept for about six weeks or more under the same experimental conditions.
—A. Rudy.

Hypophyseal plethora (Cushing's disease; pituitary basophilism) (Die hypophysäre Plethors [Cushingsche Krankheit: pituitary basophilism]). Jamin, F., München. med. Wchnschr. **81:** 1045. 1934. Abst., J. A. M. A. **103:** 794.

Jamin describes a case of the syndrome (obesity, osteoporosis, genital hypoplasia, hypertension and adynamia) that Cushing ascribes to the basophil adenoma of the anterior lobe of the hypophysis. The author emphasizes that circulatory disturbances, acrocyanosis, angiospasm and hypertension play a determining part in the syndrome, and for this reason he suggests the term "hypophyseal plethora" as an antithesis to the term "hypophyseal cachexia." He points out that the disease is the manifestation of an endocrine hyperactivity of the adenohypophysis. This hyperfunction is to be differentiated from the effects of the growth hormone, for it is rather the result of an excessive, unchecked hypophyseal stimulation of subordinate endocrine glands, particularly of the suprarenals, the posterior lobe of the hypophysis and the parathyroids, which becomes manifest as a pluriglandular disturbance involving the appearance as well as the functional activities of the organism. High voltage roentgen irradiation has been known to influence the syndrome favorably. The endocrine hyperfunction is probably the result of adenomatous or diffuse proliferation of the basophil elements of the adenohypophysis.

Problems in treatment of diabetes insipidus with extract of posterior lobe of hypophysis (Über Fragen der Hypophysenhinterlappentherapie des Diabetes insipidus). Mainzer, F., Wien. Arch. f. inn. Med. **26:** 101. 1934.

The author reports studies on 5 cases of the so-called "hypochloremic" type of diabetes insipidus. The efficacy of posterior lobe extract parenterally

and nasally administered is discussed. Voegtlin units were utilized to give more accurate measurement of the action of the extract. The "water equivalent" is that quantity of fluid by which the fluid exchange is reduced under the influence of one Voegtlin unit for each kilogram of body weight. Evidence is introduced to support the theory that there is no "dehydration" in this type of case. Patients varied in their requirement, and apparently varied from time to time during the course of the disease so that true estimation of the minimum amount of extract effective would be difficult to establish. Chronic nasal irritation sometimes developed in the cases in which the extract was administered over a long period of time by this route. The majority of cases seemed to require larger doses of extract to work effectively as time went on. At least one case, however, displayed a decreased tolerance and actually seemed to improve.—G. W. Thorn.

Necessary concurrence of thyroid in the marked adrenal cortical hypertrophy following beef anterior pituitary implants. McQueen-Williams, M., Proc. Soc. Exper. Biol. & Med. **32**: 296. 1934.

Implants of beef pituitary into normal rats induced marked adrenal hypertrophy and an increase of two or more times in weight. Implants into thyroidectomized rats had little or no effect. The cortex was chiefly involved. It is suggested that the pituitary has two adrenotropic actions, one direct and one through the thyroid gland.—M. O. L.

The control of the dermal melanophores in elasmobranch fishes. Parker, G. H. and Helen Porter, Biol. Bull. **66**: 30. 1934.

The common dogfish, Mustelus canis, has a dark phase and a light one due to the expansion and the contraction of its dermal melanophores. The dark phase is induced by pituitary secretions carried from the pituitary gland to the melanophores by the blood and lymph as described by Lundstrom and Bard. The light phase is induced through the action of contracting nerves, and is not merely the result of the absence of pituitary secretions. The expanding hormone is water-soluble. The contracting one, if there be such, is apparently not water-soluble. The dogfish is remarkable as the first form to be described in which the cutting of nerves induces a contraction of the melanophores and a consequent lightening of the skin.—Authors' Summary.

Hemorrhagic changes in suprarenal cortex of adult rats following pituitarectomy. Perla, D., Proc. Soc. Exper. Biol. & Med. **32**: 654. 1935.

Within the first 2 weeks following hypophysectomy in adult albino rats hemorrhagic changes are observed in the cortex of the suprarenal which precede the atrophy of the gland. The similarity to the changes observed soon after birth in humans is pointed out. By inference this observation tends to strengthen the hypothesis that the severe hemorrhagic involutional changes noted in early extra-uterine life may be due to the withdrawal of the maternal adrenotropic hormone of the anterior lobe.—Author's Summary.

Origin of functional differences between male and female hypophyses. Pfeiffer, C. A., Proc. Soc. Exper. Biol. & Med. **32**: 603. 1935.

Transplantation of testes of newborn male rats into the neck region of littermate females produced "takes" in 80% of 150 animals. In 48% the grafts did not interfere with normal endocrine or reproductive functions of the carriers, while in 32% the implanted testis assumed control of the sexual differentiation of the hypophysis. The male hypophysis stimulates follicular development but not luteinization in the host ovary. These hosts start constant oestrus and maintain this condition after the removal of the testicular graft. It is concluded that the cases with constant oestrus are those in which the implanted testis was sufficiently active to have a leading influence upon the hypophysis which responds with the male type of constant non-cyclic function; that the hypophysis is permanently altered; that the sex type of the hypophysis is secondary, depending upon the presence of differentiated sex glands.
—M. O. L.

Lactogenic factor of the pituitary. Riddle, O., J. A. M. A. **104:** 636. 1935. Abst., A. M. A.

The author states that a knowledge of the various responses elicited by a hormone is necessary to a wise choice of a method for its bioassay, and the "lactogenic" factor has proved to be more ancient than lactation. There are four known responses, or aspects of tissue response, to prolactin to consider for purposes of assay. These responses are lactation in mammals, growth of crop-gland in pigeons, broodiness in fowls and marked size diminution in active gonads of adult pigeons and fowl. The crop-gland response in doves or pigeons was shown to be a reliable and practicable method of assay. The induction of lactation response in pseudo-pregnant rabbits has been used for a rough bioassay (— to ++++) of the lactogenic factor, after various workers noted the unsuitability of rats and mice for this purpose. There is no evidence that the development of mammary tissue is assisted in the slightest degree by the lactogenic factor, and there is evidence that it has no such favoring effect. Some reports indicate that an unidentified pituitary factor favors mammary growth; but the lactogenic factor apparently acts on fully prepared mammary tissue solely to initiate and excite milk secretion. A group of investigators at the University of Chicago has recently proposed the hypothesis, based on experimental observations, that the lactogenic factor of the pituitary is suppressed during pregnancy by estrogenic substance, normally produced in large amounts during this period. At the same time the estrogenic factor causes growth of the mammary gland. At parturition, with loss of the placenta, the level of estrogenic substance in the blood stream drops sharply, thus permitting the release of the lactogenic factor from the pituitary. The breasts, having been prepared in the meantime, then respond to this factor with secretion of milk. Riddle, Bates and Dykshorn showed that by first causing suitable growth of the mammary substrate, lactation may be produced even in males.

The difference of response of the pituitary glands of male and female albino rats treated with the growth hormone. Rubinstein, H. S., Anat. Rec. **61:** 131. 1934.

Seventy-four albino rats were divided according to sex and each sex subdivided into three subgroups, according to weight. The lightest animals were used as test animals and the heavier rats were used as controls. At the beginning of the experiment all animals had reached the adult state, being 6 to 8 months of age. The test animals were injected intraperitoneally daily (except Sunday) with 2 cc. of growth hormone for 22 weeks. The controls were subdivided into two groups, the heavier of which received no injections, while the lighter controls received injections of a meat extract prepared and administered similarly to the growth hormones. Body weights were taken before, during, and at the end of the experiment at which time the test animals had gained significantly over their controls. The animals were then anesthetized and killed by bleeding through the carotids and their pituitary glands removed and weighed. The data thus obtained were subjected to statistical methods. It was concluded on the basis of this study that the pituitary glands of male and female albino rats respond differently to the administration of growth hormone in that the normally smaller pituitary gland of the male becomes significantly heavier while the naturally heavier gland of the female fails to increase but is somewhat retarded in its growth.—Author's Abst., Wistar Bib. Service.

General physiology of anterior hypophysis. Smith, P. E., J. A. M. A. **104:** 548. 1935. Abst., A. M. A.

Although the general physiology of the anterior hypophysis is inseparable from its special physiology, the author gives a general discussion of the recent developments of the knowledge of pituitary physiology. Experimental and other work is increasingly showing the important position which this organ occupies among the endocrine glands. There appear to be but few body functions that it does not influence, either directly or indirectly. Barger has spoken of it as "general headquarters" of the endocrine system, a characterization that aptly expresses its dominant position in this system. Undoubtedly, the large number of contributions that have been published on the anterior hypophysis within the last decade have not simplified but rather have made more complex knowledge of its physiology. The author discusses the pituitary hormones, antihormones and the species and sex variability.

Hypophyseal gonadotropic hormones. Smith, P. E., J. A. M. A. **104:** 553. 1935. Abst., A. M. A.

The author points out that work on the gonadotropic substance from the hypophysis and from other sources (from castrate and menopause urine) strongly indicates that the principle commonly designated as the gonad-stimulating principle is composed of two principles. One of these, a gametokinetic (follicle stimulating) principle, has been secured in a fair degree of physiologic purity by fractionation of the anterior hypophysis, and it is also present with little or no contamination with other hormones in the blood and urine after the menopause and ovariectomy. Work with the other principle is somewhat less satisfactory. It appears that the other factor, which may at this time be designated as a "luteinizer," causes luteinization of the ovary. It presumably acts also on the interstitial tissue of the testicles. The present indications are that in the therapy of hypogonadism due to a hypophyseal deficiency the administration of one or the other or a proper mixture of these two factors will be required to induce normal gonadal function.

The use of anterior lobe pituitary extract in the treatment of Addison's disease. Wilder, R. M., Proc. Staff Meet., Mayo Clin. **9:** 689. 1934.

Extract of anterior lobe of pituitary glands of beef, containing the growth-promoting and thyrotropic hormones, were injected daily into 2 patients with Addison's disease who were under treatment with suprarenal cortical hormone and extra salt. Both patients were less sensitive to withdrawal of the extra salt in periods when they were receiving anterior lobe extract. Also, both patients were distinctly stronger when receiving the anterior lobe pituitary extract. The observations support the view that secondary deficiency of the anterior lobe of the pituitary gland may be a factor in Addison's disease and suggest that anterior lobe pituitary hormone may be used with advantage as a supplement to cortical extract in the treatment of this disease.—Author's Abst.

Reaction of the anterior pituitaries of immature female rats to injection of pregnancy urine extracts. Wolfe, J. M., Am. J. Physiol. **110:** 159. 1934.

Thirty-one immature female rats (21 to 25 days) received from 25 to 75 units of pregnancy urine extract daily for 7 to 15 days. Thirty-three littermate sisters served as controls. The ovaries of the injected animals were markedly increased in weight, while the pituitaries were moderately increased. Histologically, the anterior pituitaries of the injected rats exhibited a loss of granules from the eosinophiles, which were also decreased in relative percentage. Most striking changes were found in the basophiles, which were enlarged and exhibited marked loss of granules. They were reduced in percentage. The percentage of the chromophobes was increased. Mitoses were more abundant in the anterior pituitaries of the injected rats. Cell counts were made on all sections studied; a total of 140,009 cells was counted.

—Author's Summary.

The anterior hypophysis of the rabbit during oestrus and pseudopregnancy. Wolfe, J. M., Doris Phelps and R. Cleveland, Am. J. Anat. **55:** 363. 1934.

During oestrus in rabbits (killed immediately after copulation) the cells of type I (eosinophiles) reach a high level in the anterior hypophysis of the rabbit. They are well packed with granules which stain intensely with orange G. During pseudopregnancy (induced by anterior lobe administration or copulation with sterile buck) there is a considerable and progressive decrease in the relative percentage of these cells until the fifth or sixth day, after which there is a restoration of these cells. During early pseudopregnancy, these cells exhibit marked granular loss; the reduced number of granules remaining in the cells takes a rather pale stain with orange G. During oestrus, the cells of type III (basophiles) reach a high level in relative percentage. A number of these cells are completely filled with violet granules; a majority exhibit varying degrees of granular reduction. During the first few days of pseudopregnancy, these cells undergo an extreme reduction in relative percentage; after the sixth day, however, there is a gradual restoration. A total of 1082 sections from pituitaries of 229 rabbits were studied. A total of 977,588 individual cells were counted.

—Authors' Abst., Wistar Bib. Service.

Chromatophorotropic principle of pars intermedia of the pituitary. Zondek, B., J. A. M. A. **104:** 637. 1935. Abst., A. M. A.

Zondek is of the opinion that the chromatophorotropic substance must be a specific hormone, for the following reasons: 1. Intermedin is lacking in the suboccipital liquor, while pitocin and pitressin are present. 2. Intermedin can be demonstrated in the pituitary colloid, while pitocin and pitressin are absent (Cushing and Goetsch). Thus, intermedin occurs independently in the organism; i.e., it is present without the oxytocic and pressor factors. 3. The quantitative proportion of intermedin to the oxytocic and pressor factors is quite different in the different lobes of the pituitary. Proof that the chromatophore-expanding substance is an independent hormone was finally brought when intermedin was isolated.

The use of insulin in malnutrition. Blotner, H., New England J. Med. **211:** 103. 1934.

This paper presents a study of the effect of subcutaneous insulin administration in 79 healthy, thin persons. Ten units of insulin, three times a day, was the standard dosage used, a few patients taking somewhat more or less than this amount. A liberal diet was employed. After insulin injections were begun, almost all the patients gained weight immediately and rapidly. The increase in weight tended to become less marked as the weight approached the standard normal weight. Few of the patients lost much of the gained weight even after a considerable period subsequent to the discontinuance of insulin. Insulin has a good general effect, most of the individuals receiving it feeling much stronger and more active than they had felt previously. The gain in weight resulting from the use of this drug depends on an increased intake, better digestion and assimilation of food. It is not due to water retention but to an actual increase in the fat deposit. The use of insulin to produce a gain in weight in certain cases of nondiabetic malnutrition is a reasonable, uncomplicated, and practical method of treatment.—Author's Summary.

The demonstration of insulin in blood by means of blood-transfusion; investigations on healthy individuals and diabetics (Über den Nachweis von Insulin im Blut mittels der Bluttransfusion Untersuchungen an Stoffwechselgesunden und Diabetikern). Boller, R., K. Uiberrak and W. Falta, Wien. Arch. f. inn. Med **25:** 1. 1934.

The authors have shown the tremendous variation of the fall of blood sugar in a series of diabetics after the intravenous injection of 1 to 3 units of insulin. Such a drop following 3 units of insulin, has been as much as 252 mg. per cent in 3 hours. They point out the extreme sensitivity in some individuals to intravenous insulin and the danger when interpretations are given in cases without normal controls. The main experiments were concerned with the transfusion of blood from normal persons into diabetics, 300 cc. of blood being used. These were made as follows: (1) the transfusion of blood from a fasting donor, (2) one and a half, (3) three and a half, (4) four and a half, and (5) five and a half hours after a heavy carbohydrate meal. The following results were obtained: (1) no effect; (2) and (3) marked fall, (4) considerable fall, (5) tremendous fall of blood sugar in the diabetics who were sensitive to insulin. When the experiments were repeated on diabetics who were insulin-resistant, there was no effect at all. Transfusions from diabetic to diabetic on the above basis produced no effect whether the donor was fasting or post-prandial. The authors conclude that insulin can be demonstrated to be present in the blood of a normal individual after heavy carbohydrate meal in the above manner. The amount of insulin present is extremely small, 1 to 2 units per 100 cc. of blood. In the blood of severe diabetics, sensitive to insulin, no insulin can be demonstrated in this manner even after a heavy carbohydrate meal. Also in severe insulin-resistant diabetics, blood after a heavy carbohydrate meal has no or else but a slight amount of insulin present.

The relation of the hypophysis, hypothalamus, and the autonomic nervous system to carbohydrate metabolism. Davis, L., Ann. Surg. **100:** 654. 1934. Abst., Surg., Gynec. & Obst. **60:** 166.

In an attempt to explain some of the vagaries of disturbed carbohydrate metabolism in cases of disturbances of the hypophysis and the related structures, the author carried out three series of experiments on cats. In the first series the pancreas was removed and later the hypophysis was damadged with the

Horsley-Clarke stereotaxic apparatus. In the second series the lesions were produced in the hypothalamus so that the hypophysis was spared, and the pancreas was then removed. In the third series, stimulation experiments were carried out on the autonomic nervous system. In the one animal of the first series that survived the operative procedures there was no ensuing evidence of diabetes. The needle had entered in the midline, passing through the third ventricle. The lesion destroyed a segment of the anterior lobe of the hypophysis and a small part of the pars nervosa, and had caused slight damage to the pars tuberalis. The infundibulum seemed to be at least partly blocked by scar tissue, and the pars tuberalis was slightly hypertrophied with acini greatly distended by colloid. The postoptic commissures, the ventral periventricular nuclei, and the gray substance of the tip of the tuber just rostrad to the infundibulum were damaged or entirely destroyed. In the light of the work of those who believe that the products of hypophyseal secretion pass from the pars intermedia by way of the tissue spaces in the pars nervosa to stimulate the tuberal and other anterior hypothalamic nuclei, it was interesting to note that in this animal the infundibulum was partially blocked and the space separating the pars intermedia from the anterior lobe was distended and contained a large amount of homogeneous material. It has been suggested that as a result of nervous impulses from the hypothalamic nuclei, ripened secretory cells are cast off, invade the pars nervosa, and become hyaline bodies which make their way through the pars nervosa toward the infundibular cavity. In the second series of the author's experiments it was found that in the animals which survived the pancreatectomy following the hypothalamic injury the hypothalamic lesions were placed so that they involved the region of the fornix and affected the perifornical nuclei. They were situated in the tuber cinereum, where their position was slightly rostrodorsolateral to the mammillary bodies. It is at about this level that the ventromedial hypothalamic nucleus lies. The lesions in the animals which did not survive the pancreatectomy did not seriously affect this region or left it entirely unscathed on one side of the hypothalamus. The evidence indicates that the hypothalamic lesion must be not only in a given area, but also bilateral and symmetrical. Stimulation of the superior cervical sympathetic ganglion or the stellate ganglion results in elevation of the blood sugar and glycosuria, but in the author's experiments in which hypothalamic lesions were produced such stimulation did not result in glycosuria. The conclusion is drawn that the glycosuria is the result of the stimulation of the hypothalamic nuclei by the hypophyseal substance which in turn results from the sympathetic stimulation.

The clinical application of duodenal extract (Macallum-Laughton) in diabetes mellitus. Duncan, G. G., N. P. Shumway, T. L. Williams and F. Fetter, Am. J. M. Sc. **189:** 403. 1935.

A child diabetic of 8, another of 13, with active tuberculosis, an adult with active tuberculosis, another admitted in coma, a boy of 16 admitted in impending coma and 2 mild diabetics of the arterio-sclerotic group (7 cases in all) are presented to illustrate that duodenal (acid extract beef mucosa) extract prevented hyperglycemia and glycosuria of any extent after the withdrawal of large doses of insulin and that subsequent great increases of carbohydrate and calories were necessary to produce hyperglycemia and glycosuria. Furthermore, better glucose tolerance curves were obtained with the extract than were obtained without it. The period of benefit following the withdrawal of the extract varied from a few days to several months. There is no evidence that the extract is of value in reducing a marked hyperglycemia or that it has any effect when given with insulin, except as stated below, but rather that its effect becomes discernible when insulin is used to control the diabetes and then omitted. Repeatedly, lower blood sugar values were obtained with the extract alone than when it was given in conjunction with insulin. In 2 patients (1 of whom is reported here) with diabetes of long standing normal glucose tolerance curves were repeatedly obtained 5 months after cessation of extract therapy. Neither hypoglycemic reactions nor any other untoward effect were noted. It seemed rather that the extract exerted an antihypoglycemic effect when large amounts of insulin were given. Respiratory quotient studies (not reported here) coincided with the behavior of the blood and urine sugars, increasing as they decreased and decreasing as they increased. Doses of 0.25 gm. of the extract, given orally, 3 or 4 times daily, were effective. Of 46 patients who received the extract, 16 were given inert material. Of the remaining 30, 12 had severe and 18 had mild diabetes. Of the 12 with severe

diabetes, 8 (4 of whom were children) showed a definite response to extract therapy, while 4 (3 adults and 1 girl of 16) gave no evidence of benefit. Of the 18 mild cases, 11 were helped and 7 were not. All of 4 of the severe diabetics who failed to benefit from the extract belong to the group of diabetics who have an extremely narrow margin of safety between hypoglycemia and hyperglycemia. Other severe diabetics requiring as much or more insulin but who have a greater margin of safety, gave spectacular response to extract therapy. The results suggest that 3 types of diabetes exist, e.g., (1) from lack of activation of the pancreatic islands by a duodenal factor, (2) from loss of islands of Langerhans and (3) an insensitiveness of the organism to insulin. The last mentioned may be subdivided to include various endocrinal imbalances. The prolonged period of apparent benefit after withdrawal of the extract suggests the possibility that the duodenal factor is to the pancreas as iodin is to the thyroid gland.—Authors' Abst.

Changes in the central nervous system resulting from convulsions due to hyperinsulinism. Grayzel, D. M., Arch. Int. Med. **54**: 694. 1934.

Fourteen rabbits were employed in these experiments. Rabbits which did not have convulsions showed no lesions in the brain. Rabbits which had slight convulsions showed minimal or no changes in the brain. Rabbits which had severe convulsions one or more times showed definite anatomic lesions in the central nervous system. The greater the number and the more prolonged the convulsions, the more severe were the lesions. The milder lesions consisted of zones containing shrunken hyperchromatic cells with corkscrew processes. The more severe lesions showed, in addition, zones of necrobiosis. The cells particularly involved were the pyramidal cells of the third and fifth cortical layers.
—Author's Summary.

The menace of diabetic gangrene. Joslin, E. P., New England J. Med. **211**: 16. 1934.

The average age of diabetic patients and their expectation of life has increased. Prevention of diabetic coma is better understood. Therefore, the danger of gangrene is greater than ever before. The author stresses the need of instruction for patients particularly in cleanliness and care of slight injuries. He discusses treatment both medical and surgical.—J. C. D.

Chronic hypoglycemia in childhood. Kramer, B., H. G. Grayzel and C. I. Solomon, J. Pediat. **5**: 299. 1934.

Two cases of persistent chronic post-absorptive hypoglycemia in children are described. The first patient, six months of age, gave a history of poor appetite, weakness, fainting spells, convulsions and an abdominal mass. On autopsy an extensive fatty infiltration of the liver but no glycogen was found. There was sufficient hepatic tissue to perform its metabolic functions except that of glycogenesis. This primary failure to form glycogen frm glucose and the consequent absence of deposits of glycogen in the liver resulted in its secondary inability to mobilize the glucose and maintain a normal blood sugar level. The authors explain the presence of the fatty infiltration of the liver on the basis of conversion of the glucose into fat since the dextrose could not be transformed into glycogen. The second case was in a girl of eight months who gave a history of "fainting spells" characterized by flaccidity of the extremities, loss of consciousness, rolling of the eyes and twitching of the eyelids. There was a persistent post-absorptive hypoglycemia manifested by the characteristic symptoms which were ameliorated by the ingestion of food. There were manifestations of retarded mentality and motor disturbances of an ataxic nature. Since to date there has been described no definite case of hypoglycemia due to central nervous lesion, the authors feel that the condition was one of pancreatic hyperinsulinism and that the central nervous disturbance was either secondary to, or independent of, the primary condition.
—M. B. G.

Alimentary cholesterolemia and blood sugar in diabetes. Sorkin, E. M. and M. I. Batuschanskaya, Acta endocrinol. ucrainica, Pp. 112. 1934.

Thirty investigations on 24 diabetic patients have shown that cholesterolemia does not correspond to the blood sugar level. It is rather correlated with the acidosis. If 50 grams of olive oil is given, the level of blood sugar is diminished, and the level of blood cholesterol is higher.—M. Breitmann.

A study of the twenty-four-hour blood sugar curve in diabetic patients. Sprague, P. H. and Dora A. Newson, Canad. M. A. J. **31**: 609. 1934.

Curves have been obtained for 8 diabetics showing varying grades of the disease. They were given 50-gram glucose meals at 8 a.m., 12 noon, and 5 p.m., and all insulin was withheld. The results support the views of Möllerström and others concerning the existence of a rhythmical cycle of carbohydrate metabolism, and suggest that in some cases such an examination may lead to a more rational treatment of the diabetes, by adjustment of insulin to times just before the periods of maximum hyperglycaemia, periods which are not always post-alimentary.—A. T. C.

Diabetes mellitus in twins. Watson, E. M., Canad. M. A. J. **31**: 61. 1934. Abst., J. Nerv. & Ment. Dis. **81**: 215.

Tangible evidence in support of the hereditary nature of diabetes mellitus is provided by the records of the occurrence of this disease in twins. Examples of the development of diabetes in both members of 21 sets of twins have been reported. A remarkable fact is that the great majority (at least 75%) of these twin diabetics are identical (or monozygotic) twins. The individual members of any set of monozygotic twins, having arisen from one fertilized ovum, are always of the same sex, frequently exhibit similar characteristics and, of course, possess identical inheritable qualities. An instance is described of identical male twins, aged 56, who resembled one another in many respects. Both developed diabetes of the same degree of severity at approximately the same time. There was not any evidence of the existence of diabetes in the immediate ancestors of these brothers, but that does not disprove the hereditary nature of these diseases because the tendency to diabetes may be transmitted as an hereditary recessive trait.

A case of osteitis deformans treated with parathormone. Colt, G. H. and A. Lyall, Brit. M. J. **2**: 10. 1933. Abst., Arch. Neurol. & Psychiat. **32**: 1086.

The authors report the treatment in a case of osteitis deformans by the administration of from 5 to 10 units daily of parathyroid extract (Collip), with periods of intermission, during two years. The treatment was augmented by sodium biphosphate, 30 grains (1.95 gm.), taken three times daily, well diluted in water, to depress the absorption of calcium in the intestine, to decrease the calcium content of the serum and to promote the excretion of calcium in the urine. Progress was noted by a series of roentgen films, which suggest definitely that there is now less calcification in the skull than there was two years before when treatment began. The patient feels better and has been able to carry on her housework and go out walking without fatigue, which had not been the case before. Her general appearance also is markedly better.

Pineal gland and development (Über die Einwirkung der Zirbel auf körperliche und geschlechtliche Entwicklung). Norlin, G. and G. Welin, Skandinav. Arch. f. Physiol. **69**: 293. 1934. Abst., Physiol. Absts. **19**: 608.

Pineal glands from male or female animals were implanted subcutaneously or intramuscularly into immature mice. No apparent change was seen either in bodily or sexual development different from that in control animals.

The presence of estrogenic substance in the pineal gland (Über das Vorkommen einer öestrogenen Substanz in der Epiphyse). Silberstein, F. and P. Engel, Klin. Wchnschr. **12**: 908. 1933.

Pineal glands of cattle were implanted into castrated mice. Prolonged positive Allen-Doisy tests were obtained throughout. Alcohol, ether, and acetone extracts made from pineal glands were found to be free from estrogenic substance. Acetone dried pineal glands were then extracted with 1% acetic acid and 1% sodium bicarbonate. While the acid extract proved ineffective marked estrogenic effect was obtained with the alkaline extracts. Intravenous injection of pineal suspension produced no gonadotropic action upon the ovaries of rabbits.—W. Saphir.

Reduction of the thymus by gonadotropic hormone. Evans, H. M. and Miriam E. Simpson, Anat. Rec. **60:** 423. 1934.

In the course of a study of the effects of chronic administration of gonadotropic hormone, it was found that chronic treatment of male or female rats, whether mature or immature, with the gonadotropic hormone found in pregnant mares resulted in atrophy of the thymus. When the testes or ovaries were removed, the gonadotropic treatment during the experiments were rejected for it is well known that the thymus recedes in inanition, cachexia and many obscure subnormal states. The testicular component involved in this reaction appears to be the interstitial tissue and not germinal epithelium, for treatment with the gonadotropic hormone after destruction of the germinal tissue by procedures which left the interstitial tissue and its dependent accessory organs intact (cryptorchidism, or vitamin E deficiency) led to the same atrophy of the thymus as it did in normal males. The results cited are based on the study of 123 animals.—Authors' Abst., Wistar Bib. Service.

The early development of the thymus glands in Amia calva. Hill, B. H., J. Morphol. **57:** 61. 1935.

Three pairs of thymus primordia are found at 6 to 6.5 mm. on the dorsal lateral ends of the second, third and fourth visceral pouches. Those on each side after fusing by growth and migration come to lie above the third visceral pouch, whence the thymus migrates upward and backward; growing in size, it stretches above the ends of all the gill pouches. It pushes inward into the mesenchyme at 12 to 13 mm. and becomes perforated and surrounded by blood vessels and connective tissue which separate it almost completely from the epithelium. No septa are found; occasionally the third primordium fails to fuse and forms a separate lobe. The early thymus is a syncytium in which are found lymphoblasts, identified by structure of the cytosome and its behavior during mitosis. Evidence is presented that lymphoblasts migrate into the thymus where they increase in number with corresponding increase in length of cytoplasmic bridges and size of intercellular spaces. At 10 mm. begins a rapid increase in size of the thymus and in number of lymphoblasts and decrease in size of the latter, culminating at 12 to 13 mm. in their transformation into thymocytes. A medulla associated with blood vessels is unmistakable at 30 mm.—Author's Abst.

The biologic effects of thymus extract (Hanson); accruing acceleration in growth and development in successive generations of rats under continuous treatment with thymus extract. Rowntree, L. G., J. H. Clark, A. M. Hanson and A. Steinberg, J. A. M. A. **103:** 1425. 1934. Abst., A. M. A.

The authors observed that thymus extract (Hanson) seems to increase the weight and growth of prepubertal and mature male rats and in mated mature female rats. The extract administered to the new-born exerts but little effect on growth and development, although earlier opening of the eyes has been noted at times. Administered intraperitoneally to parent rats it seems to increase the number and size of the litters and the birth weight of the offspring. The most striking biologic effects of the thymus extract are obtained and are most evident in the offspring following continuous treatment by intraperitoneal injection of successive generations of rats. The third generation test animals are larger at birth and evidence striking precocity in growth and development. Successive generations of rats born to thymus-injected parents evidence accruing acceleration in growth and development. Thus in the fifth generation teeth have erupted and ears opened on the first day. The eyes opened and the animals were covered with fur by the third day. The testicles descended between the fourth and fifth days and the vagina opened in 20 days. In the thymus-treated strain the offspring of the third generation have cast litters on the fortieth and forty-fifth days. The effect of thymus treatment is more marked in the offspring than in the parents. Weight curves show an accruing acceleration in each succeeding generation. The acceleration and the rate of growth and development in the untreated young born of thymus-treated ancestors is apparently not effected through the mother's milk, since in two experiments it occurred when the young were suckled by a control "wetnurse" mother and did not appear in control animals suckled by thymus-treated mothers. Thymus extracts made by Hanson's method are not all equally potent, as evidenced by one preparation secured from another source.

Interruption of thymus administration for one generation nullifies completely or at least to a large extent the effects of previous thymus administration, even though this treatment may have extended through several generations of rats. The lack of thymus effect becomes more striking in succeeding litters. Excessive amounts of thymus extract result in toxicity, as evidenced by increasing auriculoventricular dissociation and eventual heart block.

Histological variations in animal thyroids in Western Canada. Abbott, A. C. and J. Prendergast, Canad. M. A. J. **31**: 465. 1934.

The thyroid glands of 667 animals, including young calves, yearling cows, sheep, foxes, mink, buffalo, horses and old range cows were sectioned and studied as to its colloid content, vacuolation, type of cell, presence of tufting, lymphoid tissue, stroma and vascularity, normal, plus and minus system being used (in reference to textbook criteria of normality). The animals varied from about 3 months in the case of the calves to old age in old range cows and buffalo. The authors point out that a moderate range of freedom in histological classification must be allowed to take care of variations found not only in different glands but in the same gland. No gland was considered hyperplastic unless the type cell was at least low columnar. Cubical cells were considered normal and tufting was considered a definite sign of hyperplasia. One of the first things noted was that the type of cell found was not necessarily dependent on the amount of colloid present, an overabundance of colloid and columnar cells being commonly associated. Moreover, a columnar epithelium did not necessarily mean a deviation from the normal but a normal physiological change due to increased work temporarily thrown upon it. The colloid content varied with the activity of the gland, being plentiful in its quiescent stage. As age progressed the relative amount tended to increase. Peripheral vacuolation means absorption and its presence signifies that the gland is passing from a quiescent to a more active stage in its physiological cycle. Lymphoid tissue was conspicuous in its absence, being present only in foxes and mink. Nothing of importance was found as to vascularity and the stroma increased with age. Two of the most interesting groups of glands studied were those of mink and fox. These glands were obtained from animals raised under ideal hygienic conditions. From the time of their birth until their demise they had been protected from all forms of fright, excessive exertion, unhygienic conditions and had been fed a well-balanced diet. As a result one would expect to find less variations in these glands than in any other. Wide variations were found, however, in histological structures. The authors conclude that in the younger animals hyperplastic active glands are the rule, and are physiological, not pathological. Small acini and little colloid is the characteristic picture. As age advances the acini tend to become larger, varying in size and not in number, colloid increases in amount, and a picture is found more like that of the normal gland. At an older age the colloid appears to be laid down in even greater quantity, the cells tend to become flattened, interacinar fibrous tissue increased, and the generalized picture is one of a gland past its prime, sluggish, and gradually declining to decay and death.

—Authors' Abst. (abbreviated).

Carbohydrate metabolism in human hypothyroidism induced by total ablation of the thyroid gland; the blood sugar response to insulin. Abrams, M. I. and D. R. Gilligan, Am. J. M. Sc. **188**: 796. 1934

The sensitivity to insulin has been observed in non-diabetic non-hyperthyroid patients before and after the development of hypothyroidism induced by total ablation of the thyroid gland (cf. cases reported). In these patients no appreciable difference has been found in the average maximum decrease of blood sugar following the subcutaneous injection of 20 units of insulin before and after hypothyroidism developed. The average decrease in blood sugar in all studies following the injection of 20 units of insulin was 34%. Signs and symptoms of mild hyperinsulinism were manifest in patients with hypothyroidism at the same level of blood sugar as in patients with normal metabolic rates. The results indicate that the response of the sympathico-adrenal system to insulin is normal in these patients with hypothyroidism, and that there is no antagonism between the internal secretions of the normal thyroid gland and of the pancreas.—Authors' Summary.

Treatment of angina pectoris and congestive failure by total ablation of the normal thyroid gland; with particular reference to surgical technique and summary of results in rheumatic heart disease. Berlin, D. D., H. L. Blumgart, A. A. Weinstein, J. E. F. Riseman and D. Davis, New England J. Med. **211:** 863. 1934.

After discussing questions of technique the authors discuss 24 cases of rheumatic heart disease treated by operation on which a history of 4 months or more was available. Four were dead, 1 unimproved, 4 showed fair improvement and the remaining 16 were decidedly improved. These results warrant the consideration of this method when medical treatment fails to bring about improvement.—J. C. D.

The utilization of the calorigenic action of diiodothyronine and thyroxine in muscular exercise. Canzanelli, A., M. Segal and D. Rapport, Am. J. Physiol. **110:** 410. 1934.

The calorigenic action of diiodothyronine and thyroxine was studied in dogs to see whether this "waste heat" could be utilized to perform muscular work. It was found that the energy of the calorigenic action of diiodothyronine cannot be so used. There is, in addition, after giving this substance a relative "inefficiency" in the performance of muscular work compared with the animal under "basal" conditions. The same is true of thyroxine, confirming, in the case of this substance, previous work by Plummer and Boothby. In regard to the second factor—the superimposed "inefficiency," diiodothyronine and thyroxine appear to differ from meat protein and tyrosine.—A. Canzanelli.

Effect of experimentally produced hyperthyroidism upon the reproductive and associated organs of the male rat. Cohen, Rose S., Am. J. Anat. **56:** 143. 1935.

Mature and immature male rats were fed desiccated thyroid gland for varying lengths of time. Their testes and seminal vesicles and prostate, adrenal and pituitary glands were compared with those of normal litter mates with reference to relative weight and histological appearance. The testes and pituitary and adrenal glands were found to exceed those of the controls in relative weight. The seminal vesicles and prostate glands were proportionately smaller in the thyroid-fed animals. Histologically, only the mammary and pituitary glands differed from those of control animals. The mammary gland gave evidence of a cellular reorganization in the hyperthyroid animals. The pituitary glands showed an increase in basophile cells in these animals, and were found to be more potent than those of the normal animals in stimulating precocious sexual maturity in immature female rats. The animals bred and fathered normal litters regardless of whether the hyperthyroid condition was induced before or after puberty. The results are believed to be due to a partial elimination of testicular hormone by the heightened rate of metabolism resulting from thyroid feeding.—Author's Abst., Wistar Bib. Service.

Progressive exophthalmos following thyroidectomy. Des Brisay, H. A., Canad. M. A. J. **31:** 389. 1934.

Three such cases are reported. Two had definite low basal metabolic rate, and the third a normal rate. In all three exophthalmos was present prior to operation.—A. T. C.

Diuresis of hyperthyroidism. Dix, A. S., J. M. Rogoff and B. O. Barnes, Proc. Soc. Exper. Biol. & Med. **32:** 616. 1935.

The diuresis produced in normal animals by thyroid administration fails to occur in pancreatectomized dogs although the metabolic rate is increased.
—Authors' Summary.

Exophthalmic goiter before one year of age. Elliott, P. C., J. Pediat. **6:** 205. 1935.

A case is reported of a two-and-one-half-year-old girl with severe exophthalmic goiter in whom symptoms began when she was six months old. Iodine medication and radiation were of no avail hence surgery was resorted to. Mild hypothyroidism resulted.—M. B. G.

Di-iodotyrosine and thyroid function. Elmer, A. W., Quart. J. Exper. Physiol. **24**: 95. 1934.

In experiments on 36 guinea pigs it was found that hyperfunction in the thyroid produced by administration of thyrotropic hormone can be inhibited by administration of di-iodotyrosine, but an identical effect is produced by potassium iodide in equivalent dosage. Evidence is presented to show that di-iodotyrosine is readily broken down in the body. The effects of di-iodotyrosine in inhibiting hyperthyroidism can be most simply and reasonably explained by the hypothesis that the breakdown of the compound releases iodine which acts in a non-specific manner.—Author's Summary.

Carbohydrate metabolism in human hypothyroidism induced by total thyroidectomy; the glucose tolerance curve and the fasting serum sugar concentration. Gilligan, D. R., M. I. Abrams and Beatrice Stern, Am. J. M. Sc. **188**: 790. 1934.

A study of the carbohydrate metabolism in 13 thyroidectomized patients is reported. The fasting serum sugar concentration was found normal in non-diabetic patients with hypothyroidism induced by total thyroidectomy. The postoperative sugar values tended to be slightly lower than those obtained before total thyroidectomy. The glucose tolerance was normal in non-diabetic patients with induced hypothyroidism. The hyperglycemia produced by the glucose was usually slightly less after total thyroidectomy than pre-operatively. One diabetic patient and one patient with hyperthyroidism showed abnormal rises in blood sugar following glucose ingestion before operation; after hypothyroidism was induced, both of these patients showed marked decreases in the degree of hyperglycemia following glucose. The findings indicate that the carbohydrate metabolism is not significantly influenced by hypothyroidism induced by total thyroidectomy except when a derangement of carbohydrate metabolism is evident prior to operation.—R. G. H.

The cellular cycle, the Golgi apparatus and the phenomenon of reversal in the human thyroid parenchyma. Gillman, J., Anat. Rec. **60**: 209. 1934.

In Golgi preparations according to Da Fano's method three distinct cell types can be recognized in the human thyroid parenchyma, viz., anabolic, katabolic and resting. Each of these cell types has a characteristic morphology of cell form, volume, and cytological content. The volume more than trebles itself from the resting stage to that of pouring out its secretion. The changes which occur in the Golgi apparatus of the thyroid cell during secretory activity are similar to those changes which occur in exocrine glands. True "reversal" of the Golgi apparatus does not exist in normal or hyperactve human thyroid glands. Since "reversal" does not exist in the human thyroid cell, there is no morphological evidence that there is reversed secretory polarity in the thyroid gland. The symptoms of exophthalmic goiter then cannot be explained as due to a precocious secretion entering the blood stream, for even in exophthalmic goiter "reversal" of the Golgi apparatus does not occur.

—Author's Abst., Wistar Bib. Service.

Clinical hyperthyroidism associated with a normal basal metabolic rate. Gordon, S. and R. R. Graham, Canad. M. A. J. **32**: 162. 1935.

An analysis is presented of 71 cases of clinical hyperthyroidism with normal metabolic rates (normal basal readings being considered as from —10 to +15%). Seventeen of the cases showed diffuse, and 54 nodular changes in the thyroid. Only one subject in each group was male. The authors consider that bilateral resection of the thyroid is the operation of choice in such patients. The amelioration of symptoms is higher in the group with nodular goiter. In no case of the series was the patient worse for operation, in 45 the condition was cured, and in 16 there was some improvement.—A. T. C.

Total ablation of the thyroid gland in the treatment of angina pectoris and congestive heart failure. Hepburn, J., Canad. M. A. J. **32**: 390. 1935.

Encouraging results were obtained in 5 cases of angina pectoris, but depressing results in 4 cases of congestive heart failure. All the latter were very severe cases of recurrent and persistent failure.—A. T. C.

Division and ligation of superior and inferior thyroid arteries in treatment of angina pectoris; report of case. Horgan, E. and J. A. Lyon, M. Ann. District of Columbia, **3:** 123. 1934. Abst., J. A. M. A. **103:** 139.

In studying a group of patients from 5 to 10 years after thyroidectomy had been performed on account of persistent or recurrent hyperthyroidism, Horgan and Lyon observed that the patients who had had a subtotal thyroidectomy with ligation of both superior and both inferior thyroid arteries did not show any evidence of hyperthyroidism and that the tachycardia or auricular fibrillation had ceased. They conclude that stopping the effects of hyperthyroidism was not entirely due to removal of the major portion of the thyroid, but that the division and ligation of the superior and inferior thyroid arteries cut the pathway of stimuli from the sympathetic nervous system to the thyroid and consequently prevented regeneration of the tissue that was allowed to remain, thus avoiding overactivity of the remaining tissue by stimulation. The effect of this operative procedure was also shown to lower the basal metabolic rate, to lower the circulatory demands and to lighten the work of the heart. Because the results of this operation had been so striking, the authors used a similar method in a case of congestive heart failure and angina pectoris; that is, cutting off most of the blood supply and cutting the pathways of stimuli to the thyroid by dividing both superior and both inferior thyroid arteries at one operation. The patient has been relieved of anginal failure and has enjoyed relatively active life for four months.

Symptoms and treatment of hyperthyroidism (Zur Klinik und Therapie der Hyperthyreosen). Jagic, N., Wien. klin. Wchnschr. **45:** 225. 1932.

The author, though surgically inclined in the management of Graves' disease, is conservative in conclusions. He favors careful individualization in treatment, with a trial during a period of two or three months by nonoperative measures such as diet, medicaments, and radiation. If within the allotted time the patient is refractory to other measures, thyroidectomy is advised.—I. B.

Circumscribed myxedema. Netherton, E. W. and B. E. Mulvey, J. A. M. A. **104:** 1492. 1935. Abst., A. M. A.

The authors report six cases of circumscribed myxedema of the plaque type. In all instances the myxedematous plaques developed after the initial attack of hyperthyroidism. In the third, fifth and sixth cases the lesions appeared simultaneously with recurrent hyperthyroidism, while in the first case the lesions were accompanied by symptoms of transitory hypothyroidism prior to the development of recurrent hyperthyroidism. In the second case the plaques developed six years after a second thyroidectomy, while in the fourth case the plaques of myxedema were associated with definite signs of hypothyroidism, which appeared two years following thyroidectomy. In four cases in which the authors have been able to make observations for several months, the plaques have remained unchanged in two instances, and in the other two the lesions have gradually become smaller. Transitory auricular fibrillation developed following thyroidectomy in the third case. The marked edema of the legs such as is frequently observed in hyperthyroidism was not present in any of these cases. The lesions of circumscribed myxedema of the skin associated with hyperthyroidim may appear as nodules or large plaques. They invariably involve the skin in the pretibial regions. The second case is an example of the distribution in large plaques. The lesions in the remaining five cases presented the more common nodules or smaller plaques. In all probability circumscribed myxedema of the skin associated with hyperthyroidism is not as uncommon as the reports in the literature would indicate. Since this condition gives very little discomfort, the patient and the physician give little consideration to these cutaneous lesions. This is especially true if the physician is not particularly interested in dermatology.

The thyroid gland in mental deficiency; a histological study. Newman, J. L., J. Ment. Sc. **79:** 464. 1933. Abst., Arch. Neurol. & Psychiat. **32:** 642.

Newman reports a histological study of the thyroid glands of 90 mentally deficient children between the ages of 1 and 19, who died at the Fountain Mental Hospital in England. In clinical analysis of the cases he uses Tredgold's classification of primary and secondary mental deficiency. By primary

mental defect he means those conditions caused by some anomaly or defect of the germ plasm, while secondary mental deficiency is due to traumatic, toxic and infectious agents. Sixty-five cases were in the primary group. The author gives a thorough analysis of the cases from the point of view of the histologic picture, clinical aspects, age at death, state of nutrition and diet. He emphasizes the extraordinary variations in the histologic picture in the so-called normal thyroids, and finds the same variation in the thyroids of mentally deficient children. No consistent findings were established correlating mental deficiency with a specific histologic abnormality of the thyroid glands. He conservatively remarks that there is evidence of qualitative and quantitative lack of parenchyma, suggesting a diminution of the function of the thyroid gland. The thyroid glands of children usually show a hyperplasia which is not seen in adults. The state of nutrition has no connection with the histologic appearance of the thyroid gland. There was no correlation between the thyroid and the thymus glands. The review of the subject occupies forty pages and is done with great care and thoroughness.

Effect of thyreotropic hormone and of desiccated thyroid upon creatine and creatinine excretion. Pugsley, L. I., E. M. Anderson and J. B. Collip, Biochem. J. **28**: 1135. 1934. Abst., Physiol. Absts. **19**: 604.

The creatine excretion of normal rats was increased by feeding desiccated thyroid, reached a peak at the 10th day, and then gradually fell whilst the metabolic rate was still rising. Six units of thyreotropic hormone in the normal rat, and 1 unit in the hypophysectomized animal, produced significant increase of creatine excretion. Creatine excretion was similarly increased in the dog. Purified extracts of the growth and adrenalotropic hormones, and boiled thyreotropic extract, were without effect upon the creatine excretion of normal rats. Antithyreotropic substance, which antagonized the metabolic stimulus of thyreotropic hormone, did not prevent an increase of urinary creatine excretion.

The effect of thyroidectomy and thyroxine on the response of the denervated heart to injected and secreted adrenine. Sawyer, M. E. MacK. and M. G. Brown, Am. J. Physiol. **110**: 620. 1935.

A study was made of the response of the denervated heart to injected and secreted adrenine before and after thyroidectomy and thyroxine. Cats were used exclusively. In 6 animals intravenous injection of a standard adrenine solution produced a practically constant increase in heart rate when administered on different days or twice on the same day. Similarly, the response of the denervated heart to adrenine secreted after a standard exposure to cold (4 cats) or to exercise (4 cats) was very constant on different days. After thyroidectomy a lowering of the basal heart rate was observed in most of the above animals but the maximal effect was not apparent for several days. Removal of the thyroid gland was followed in all 6 cats by a 30 to 60% decrease in the rate response of the heart to a standard solution of injected adrenine. In the experiments with secreted adrenine thyroidectomy was followed by approximately a 50% decrease of the heart response to standard cold and exercise stimuli. In all cases the decrease in response did not reach its maximum for some days. After thyroidectomy a decrease in oxygen consumption accompanied the decrease in rate response of the heart but usually followed the latter. In some animals a partial return of the oxygen consumption and of the rate response to secreted and injected adrenine took place 9 to 14 days after removal of the thyroid. The original response of the heart to both injected and secreted adrenine was restored in several animals by doses of thyroxine which raise the metabolism to its normal level. In three animals sufficient thyroxine was given to raise the metabolism above normal, and the response of the heart to injected and secreted adrenine was correspondingly increased. After thyroidectomy a change in the quality of the heart sounds in response to injected adrenine was noted in all 6 animals. In 2 of these the original quality was restored after the administration of thyroxine. On comparison of the results obtained with injected and secreted adrenine, the suggestion is offered that the interrelationship that exists between the thyroid and adrenals is due to an altered sensitization of the structures on which adrenine acts rather than to an altered output from the adrenal medulla. A tentative explanation is given for the relief of pain in angina pectoris by total thyroidectomy.

—Authors' Summary.

Myxedema and diabetes mellitus; with the report of a case. Shepardson, H. C. and G. K. Wever, Internat. Clin. **4**: 133. 1935.

A review of the literature pertaining to the metabolism of carbohydrate in hypothyroid states is presented and the cases of myxedema and diabetes mellitus occurring in the same individual are collected. The anamnesis of a patient having myxedema and later developing diabetes mellitus is recorded, together with some observations made on the patient. The causal relationship between the two diseases is discussed. The coincidental occurrence of myxedema and diabetes mellitus is no more nor less than could be predicted from the occurrence of either disease alone. No reason seems apparent, from a review of the subject and a study of this case, to suppose that the secretions of the thyroid gland have any influence on the incretory function of the pancreas.—Authors' Summary.

Further studies on the effect of cod liver oil on the thyroid gland. Sherwood, T. C. and W. G. Luckner, J. Nutrition, **9**: 123. 1935.

Rats were given from 0.1 cc. to 0.3 cc. of cod liver oil, carotene and haliver oil daily. One group received the equivalent of cod liver oil iodine daily in the form of potassium iodide. The effect of excessive vitamin A is apparently demonstrated. The iodine contained in cod liver oil apparently produces no change in the thyroid structure. However, iodine equal to the amount found in cod liver oil administered in the form of potassium iodide caused a colloid retention. Fifty adult male and female albino rats were used in this investigation.
—Authors' Abst., Wistar Bib. Service.

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